FDA Briefing Document

Oncologic Drugs Advisory Committee

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NDA 206317

Triferic® ("soluble ferric pyrophosphate"; SFP)

Rockwell Inc.

DISCLAIMER STATEMENT

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought the Triferic application seeking approval for the treatment of iron loss or iron deficiency to maintain hemoglobin in adult patients with hemodialysis-dependent chronic kidney disease and to reduce the prescribed dose of erythropoiesis stimulating agent (ESA) required to maintain desired hemoglobin levels to this Advisory Committee in order to gain the Committee's insights and opinions. The background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

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Executive Summary:

Triferic ("soluble ferric pyrophosphate"; SFP) is submitted for approval as a parenteral iron agent for use in the chronic treatment of iron loss, maintenance of hemoglobin, and reduction of erythropoiesis stimulating agent (ESA) use in adults with hemodialysis-dependent chronic kidney disease. Triferic is supplied as single use 5mL ampules each containing 27.2 mg elemental iron (5.44 mg iron/mL) in water for injection. For use in hemodialysis (HD) a 5 mL SFP ampule is added to 2.1-2.5 gallons of liquid bicarbonate concentrate. The resulting mix is then added to the remainder of the dialysis solution components diluting the iron further. The sponsor indicates that addition of a 5 mL SFP ampule to 2.5 gallons of liquid bicarbonate concentrate generates a hemodialysate with a final concentration of 110 micrograms or 2 micromoles of SFP iron per liter of dialysate. This dosing was studied in the clinical trials.

The efficacy of Triferic was evaluated in two randomized controlled phase 3 clinical trials of identical design in adult patients with hemodialysis-dependent chronic kidney disease (HDD-CKD) (305 patients in SFP-4 and 294 patients in SFP-5) for the proposed indication for the treatment of iron loss or iron deficiency to maintain hemoglobin. Each study was a multicenter, randomized, single-blind, placebo-controlled study in iron-replete patients with HDD-CKD. Study patients received SFP in dialysate at the concentration of 110 μg iron/L or standard dialysate without SFP as placebo during each hemodialysis for 3 or 4 times per week. Randomized treatment duration was planned for up to 48 weeks. The mean treatment duration in the randomized phase was 157.7 days in the SFP group and 164.6 days in the placebo group in study SFP-4 and 161.2 days in the SFP group and 157.9 days in the placebo group in study SFP-5. About 50% of study patients received study treatment for ≥20 weeks and 20% of study patients received study treatment for 44-47 weeks in the randomized phase.

The primary efficacy endpoint was the change in mean hemoglobin (Hgb) from baseline to the end of treatment period (last one-sixth of the randomized treatment period). In Study SFP-4, the mean hemoglobin decreased 0.03 g/dL in the SFP group as compared to 0.38 g/dL in the placebo group in the ITT population. In Study SFP-5, the mean hemoglobin decreased 0.08 g/dL in the SFP group as compared to 0.44 g/dL in the placebo group in the ITT population. The primary efficacy analysis used an ANCOVA analysis with baseline hemoglobin as the covariate. The treatment difference in hemoglobin calculated as least square (LS) mean difference was 0.35 g/dL in each study between the SFP and the placebo groups and was statistically significant (p=0.01) in both studies. The results of additional analyses in MITT population and secondary endpoints in changes in TSAT and serum ferritin level from baseline to the end of treatment were consistent with the results from the primary efficacy analysis in both studies.

Although treatment duration was planned for up to 48 weeks, it is notable that only a minority of patients completed full 48 weeks treatment, due in large part to protocol-mandated change in anemia management (involving changes in ESA and/or iron dosing). In Study SFP-4 these included 45.4% of patients in the SFP group and 53.6% in the placebo group; in Study SFP-5 these included 46.3% of patients in the SFP-group and 61.2% in the placebo group. A greater percentage of patients in the SFP group (27%) as compared to the placebo group (20.9%) had

hemoglobin >12 g/dL prior to withdrawal and more subjects in the placebo group as compared to the SFP group (17.6% vs. 11.2%, respectively) had hemoglobin <9 g/dL in Study SFP-4. Similarly, in Study SFP-5, there were more subjects with hemoglobin < 9 g/dL prior to withdrawal in the placebo group as compared to the SFP group (23.1% vs. 15%, respectively) and more subjects had hemoglobin >12 g/dL in the SFP group as compared to the placebo group (21.8% vs. 14.3%, respectively) prior to withdrawal.

The submission also includes a Phase 2 study (NIH-FP-01) to support a labeling statement for reduction of erythropoiesis stimulating agent (ESA) in these patients. In this multicenter, randomized, double-blind, placebo-controlled study in 103 iron-replete patients with HDD-CKD patients received either SFP or placebo during dialysis. The mean treatment duration was 212 days in the SFP group and 222 days in the placebo groups. The primary efficacy endpoint was the percent change from baseline in ESA dose at the end of treatment. The results showed that the subjects receiving SFP had a mean increase of 7.3% in prescribed ESA dose at end-of-treatment as compared to a mean increase of 37.3% in the placebo group (p=0.045). However, the subjects receiving SFP had a mean 12.5% increase in actual ESA dose as compared to a mean 42.2% increase in the placebo group and the differences between the two treatment groups did not reach statistically significant (p=0.098). The secondary efficacy endpoint analysis showed a similar distribution of changes in the prescribed ESA dose between the SFP and the placebo groups (p=0.915). The NIH-FP-01 study protocol stated that this study was exploratory in nature and statistical tests were considered to be descriptive rather than conclusive. No formal sample size determination was provided in the protocol.

The safety of Triferic was evaluated primarily in two randomized placebo-controlled phase 3 clinical trials (SFP-4 and SFP-5) in patients with HDD-CKD (total of 292 patients received SFP). Overall treatment-emergent adverse events (TEAEs) were reported at similar rates for the SFP-treated patients and the placebo-treated patients (78.4% and 75.3%, respectively) during the studies. Non-fatal treatment-emergent serious adverse events (SAEs) were reported at similar rates between the two groups (24.0% in SFP-treated patients and 25.3 % in the placebo-treated patients). Thirteen (4.5%) patients had at least one TEAE that leading to treatment discontinuation permanently in the SFP group as compared to 7 (2.4%) the placebo group in the clinical trials.

A total of 17 deaths were reported in the two phase 3 clinical trials including 12 (4.1%) among the SFP-treated patients and 5 (1.7%) among the placebo-treated patients. Among the death cases, the duration on study treatment ranged from 8 to 328 days in the SFP-treated patients and 27 to 227 days in the placebo-treated patients. Time to event leading to deaths since the last hemodialysis with study drug ranged from 1 to 15 days in the SFP-treated patients and 1 to 3 days in the placebo-treated patients. Almost all patients had significant underlying cardiac conditions in addition to end-stage renal disease. Six patients in the SFP group and one patient in the placebo group died at home or nursing home without detailed information provided. The events leading to deaths were cardiac arrest in 8 cases (6 in SFP-treated patients and 2 in placebo-treated patients), sudden deaths or unknown cause in 5 cases (4 in SFP-treated patients and 1 in placebo-treated patients), acute MI in 3 cases (1 in SFP-treated patients and 2 in placebo-treated patients), and one case of bronchopneumonia in the SFP group. No deaths were

considered to be related to the study treatment by investigator and cases could be most likely attributed to co-morbid disease and/or disease progression.

In the two phase 3 clinical trials, suspected hypersensitivity reaction was reported in one (0.3%) patient in the SFP group as compared to none in the placebo group (0%). The event was considered as moderate and related to study drug. Five additional cases of suspected hypersensitivity reaction were reported in phase 2 and the phase 3 open-label extension treatment studies. Overall, six (0.4%) cases of suspected hypersensitivity reactions were reported in 1411 SFP-treated patients in clinical trials in the SFP development program. In 2 of the 6 cases events occurred at the first dose, were considered to be study drug related and study treatment was discontinued permanently. The remaining 4 patients continued the SFP treatment without recurrent events and the events were not considered to be related to the study drug. Occurrence of other adverse events of special interest, including intradialytic hypotension, composite cardiovascular events, hemodialysis vascular access thrombotic event, and systemic or serious infection, were similar between the SFP group and the placebo group. A total of 1411 patients were exposed to Triferic in all clinical trials including open-label extension studies. The safety profile of Triferic in those patients was similar to that observed in Phase 3 clinical trials.

1. Introduction

The sponsor has developed Triferic (referred to as "soluble ferric pyrophosphate" or SFP) for use in the chronic treatment of iron loss, maintenance of hemoglobin, and reduction of ESA use in adults who are hemodialysis-dependent due to chronic kidney disease. As rationale for product development the sponsor states that the administration of iron via dialysate approach "is intended to provide a slow, measured, continuous transfer of iron to the patient in contrast to the more intermittent bolus delivery used with IV macromolecular iron complexes." The sponsor states the following in the Indications section of the proposed labeling:

> "Triferic® is a sterile concentrate solution in water for reconstitution in the bicarbonate concentrate component of the hemodialysis solutions. Triferic® provides bioavailable iron for the treatment of iron loss or iron deficiency to maintain hemoglobin in adult patients with hemodialysis-dependent stage 5 chronic kidney disease (CKD 5HD).
>
> Triferic® has been shown to reduce the prescribed dose of erythropoiesis stimulating agent (ESA) required to maintain desired hemoglobin levels. An average dose reduction of 35% in ESA requirement was observed compared to placebo in a single well-controlled study. Doses of ESA should be titrated accordingly."

2. Background

Patients with chronic kidney disease who are on hemodialysis (CKD-HD) have an ongoing need for replenishment of body iron due to loss of iron during dialysis and may develop anemia due to low body iron stores and impaired utilization of iron. In patients with CKD-HD, oral iron is poorly absorbed. Consequently, in these patients any iron deficit is typically treated with parenteral iron administration. Currently there are several iron products for intravenous (IV) administration approved in the U.S.for this population. These include INFeD and Dexferrum (iron dextran), Ferrlecit (sodium ferric gluconate complex), Venofer (iron sucrose), Injectafer (ferric carboxymaltose) and Feraheme (ferumoxytol). Intravenous iron products have been associated with anaphylactic-type reactions. Iron dextran products (INFeD and Dexferrum) have a boxed warning for anaphylactic-type reactions. Ferrlecit, Venofer, Feraheme and Injectafer have bolded warnings for hypersensitivity reactions.

The sponsor describes Triferic (SFP) as a mixed ligand iron compound in which iron (III) is covalently bound to pyrophosphate and citrate. Each 5 mL single use ampule contains 27.2 mg elemental iron (5.44 mg iron/mL) in water for injection. For use in hemodialysis (HD) a 5 mL

SFP ampule is added to 2.1-2.5 gallons of liquid bicarbonate concentrate. The resulting mix is then added to the remainder of the dialysis solution components diluting the iron further. The sponsor indicates that addition of a 5 mL SFP ampule to 2.5 gallons of liquid bicarbonate concentrate generates a hemodialysate with a final concentration of 110 micrograms or 2 micromoles of SFP iron per liter of dialysate. The sponsor states that SFP is transferred from the dialysate to the blood compartment by diffusive transport across the dialyzer membrane over the entire three- to four-hour HD treatment. SFP (Mr about 1000 daltons) is of a molecular size similar to vitamin B12 and is transferred across the dialyzer membrane to the patient at about 50% the rate of urea and other low molecular weight solutes. Triferic is intended to be included in the hemodialysate at each hemodialysis procedure for as long as patients are receiving maintenance hemodialysis therapy for CKD.

Regulatory History
Ferric pyrophosphate (FePPi) was initially submitted in August 1996 under an investigator-sponsored Investigational New Drug (IND) application. The product was transferred to the current applicant, Rockwell Medical, in 2002 and the product name was subsequently changed to Soluble Ferric Pyrophosphate (SFP). There have been several meetings and advisory and informational communication between the Agency and the sponsor during development. The applicant submitted a Special Protocol Assessment (SPA)for the pivotal protocol (SFP-4 and SFP-5); however, agreement was not reached. The protocol was revised further following discussion with the Agency. A pre-New Drug Application (NDA) meeting was held with the applicant in September 9, 2013.

Triferic has not been approved for marketing anywhere in the world.

3. Clinical/Statistical - Efficacy

To support the proposed indication for the treatment of iron loss or iron deficiency to maintain hemoglobin in adult patients with hemodialysis-dependent chronic kidney disease (HDD-CKD). the sponsor has submitted 2 pivotal randomized, single-blind, placebo-controlled, parallel group studies of essentially the same design (SFP-4 and SFP-5), each with an open-label extension following the randomized treatment period. To support labeling to reduce the prescribed dose of erythropoiesis stimulating agent (ESA) required to maintain desired hemoglobin level the sponsor submitted one Phase 2 trial (NIH-FP-01).

The major results of these studies are summarized in this document.

3.1 Studies SFP-4 and SFP-5

3.1.1 Study Protocol

SFP-4 and SFP-5 had identical study protocols. The following is a summary of the study protocols.

Study title

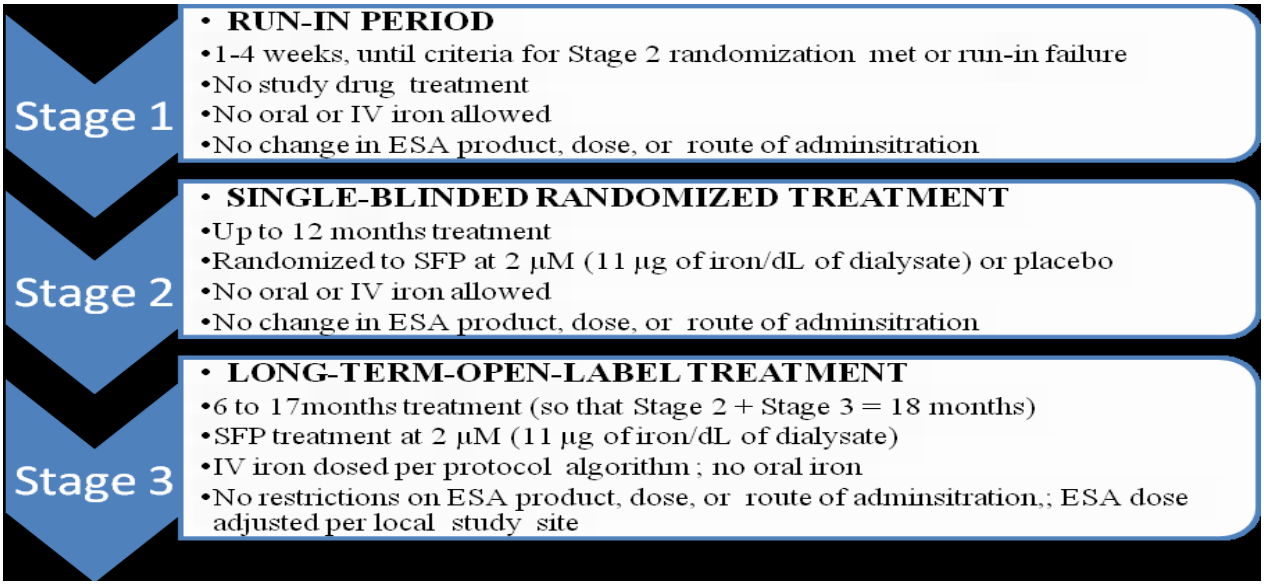
A Randomized, Placebo-Controlled, Phase 3 Study of Dialysate Containing Soluble Ferric Pyrophosphate (SFP) in Chronic Kidney Disease Patients Receiving Hemodialysis: The Continuous Replacement Using Iron Soluble Equivalents (CRUISE 1 or CRUISE 2) Study

Study design

The two studies were a multicenter, randomized (1:1), single-blinded (only the study patients were blinded to treatment assignment), placebo-controlled, Phase 3 studies to evaluate the efficacy and safety of SFP in adult patients with hemodialysis-dependent CKD (HDD-CKD).

Each study had three sequential stages following the screening period (see Study Flow Diagram below):

Figure 1. Study Flow Diagram



The protocols provided the following restrictions for iron and ESA treatment during the studies in order to minimize the potential confounding effect of concomitant iron therapy and ESA on hemoglobin and iron parameters:

- Oral iron therapy was prohibited throughout the entire study duration, including the screening period
- Intravenous (IV) iron was prohibited during the screening period and the run-in and randomized treatment stages of the study, but permitted during the long-term open-label treatment extension stage of the study, during which time IV iron could be administered according to the protocol-specified IV Iron Administration Algorithm.
- During the run-in stage, and the randomized treatment stage the product, route of administration and dose of the erythropoiesis stimulating agent (ESA) were not to be

changed. There were no restrictions on the ESA product, route of administration, and dose in the open-label treatment extension stage.

Patients were expected to undergo hemodialysis three or four times each week throughout the study. The duration of each dialysis session and the dialysate flow rate were determined by the Investigator and could be changed at any time based on individual patient needs.

Hematology and iron parameter laboratory evaluations included weekly hemoglobin (Hgb), every-other-week pre-dialysis serum ferritin, reticulocyte hemoglobin content (CHr), and serum iron panel (serum iron, UIBC, transferrin, and calculated TIBC and TSAT), and every-four-week post-dialysis serum iron panel.

Patients were to be withdrawn from the study for the following reasons:

For Stage 1 (Run-in phase):

- RBC or whole blood transfusion.
- Medical necessity for IV iron, defined as serum ferritin < 100 μg/L over ≥ 1 week confirmed by ≥ 2 consecutive measurements.

For Stage 2 (Randomized phase):

- RBC or whole blood transfusion.
- Study drug administration was suspended for ≥ 12 consecutive weeks for any reason.
- Signs or symptoms of unacceptable toxicity attributed to study drug administration occurred.
- ESA dose changed that was NOT required per Protocol-Mandated Change in Anemia Management for either ESA dose (i.e., for Hgb < 9.0 g/dL or > 12.0 g/dL confirmed by a consecutive repeat value obtained between ≥ 1 day and ≤ 2 weeks after the first value), unless each of the following conditions were met:
  - ESA dose change was ≤35% from the average prescribed weekly dose,
  - ESA dose change occurred ≥12 weeks after an prior ESA dose change,
  - Baseline ESA dose was resumed within 11 calendar days of the change.
- One time IV iron dose >125 mg or multiple IV iron administrations of any dose, that were NOT required Protocol-Mandated Change in Anemia Management (i.e., for ferritin <100 μg/L over ≥ 1 week confirmed by ≥ 2 consecutive measurements)

For Stage 3 (Open-label extension phase):

- Study drug administration was suspended for ≥ 12 consecutive weeks for any reason.
- Signs or symptoms of unacceptable toxicity attributed to study drug administration occurred.

Criteria for transition from Stage 2 to Stage 3:
Patients who were withdrawn from Stage 2 were eligible to transition to Stage 3 if they met one of the following criteria, AND less than four weeks had elapsed since withdrawal from Stage 2:

- completed the full duration of Stage 2 and less than four weeks had elapsed since completion of Stage 2, OR

- required protocol-defined Protocol-Mandated Change in Anemia Management for ESA dose (i.e., Hgb < 9.0 g/dL or > 12.0 g/dL confirmed by a consecutive repeat value obtained between ≥ 1 day and ≤ 2 weeks after the first value), OR
- required protocol-defined Protocol-Mandated Change in Anemia Management for IV iron (i.e., serum ferritin < 100 μg/L over ≥ 1 week confirmed by ≥ 2 consecutive measurements), OR
- Hgb >11.5 g/dL over ≥ 1 week confirmed by ≥ 2 consecutive weekly measurements AND an associated increase in Hgb by ≥ 1 g/dL over 4 weeks.

Study population

Inclusion criteria:

Stage 1 selection:

1. Adult subject ≥ 18 years of age undergoing chronic hemodialysis three or four times per week for chronic kidney disease (CKD) for at least 4 months, and expected to remain on hemodialysis three to four times weekly and be able to complete the duration of the study.
2. Received IV iron therapy between 6 months and 2 weeks prior to enrollment in order to replace iron losses resulting from hemodialysis procedure.
3. Mean Screening Hgb ≥ 9.5 to ≤ 11.5 g/dL.
4. Mean Screening TSAT ≥ 15% to ≤ 40%. Excursion of either TSAT or ferritin by ≤10% outside these ranges permitted only if all other inclusion/exclusion criteria are met.
5. Mean Screening serum ferritin ≥ 200 to ≤ 800 μg/L. Excursion of either TSAT or ferritin by ≤10% outside these ranges permitted only if all other inclusion/exclusion criteria are met.
6. If being administered epoetin, darbepoetin, or CERA, epoetin dose ≤ 45,000 U/week, darbepoetin dose ≤ 200 μg/week, or CERA dose ≤ 400 μg/month during the four weeks prior to enrollment.
7. Minimally adequate *measured* dialysis dose defined as:
    a. For three times weekly dialysis, URR (urea reduction ratio) ≥ 65%, or single-pool Kt/V (dialyzer clearance of urea multiplied by dialysis time, divided by patient's total body water) ≥ 1.2, or KIDt/V (online dialyzer clearance measured using ionic dialysance multiplied by dialysis time, divided by patients total body water) ≥ 1.2, or
    b. For four times weekly dialysis, single-pool Kt/V ≥ 0.9.
8. Stable dialyzer blood flow rate that is generally ≥ 250 mL/min and acceptable to the Investigator.
9. Vascular access for dialysis that will be used upon enrollment with stable function in the judgment of the Investigator without requiring medical or surgical thrombectomy for restoring patency or antibiotics for confirmed infection over the 3 months prior to enrollment, and consisting of either a tunneled catheter (internal jugular or subclavian) or

an arteriovenous (AV) fistula or graft. The percent of patients enrolling in Stage 1 with a catheter will be limited to 20% of the enrolled population within each individual country.

10. Female subjects must be either amenorrheic for ≥ 1 year or agree to not become pregnant by continuous use, during sexual activity, of an effective birth control method acceptable to the Investigator from enrollment in Stage 1 through the duration of their participation on study.
11. Must be willing and able to provide written informed consent directly or through their authorized representative.

Stage 2 patient selection:

1. Patient currently enrolled in the Stage 1 run-in period of study
2. Undergoing chronic hemodialysis three or four times per week for chronic kidney disease (CKD), and expected to remain on hemodialysis three to four times weekly and be able to complete duration of the study.
3. Mean Hgb ≥ 9.5 to ≤ 11.5 g/dL over the three most recent consecutive every-week measurements prior to randomization.
4. Stable Hgb defined as ≤ 1.0 g/dL difference between the maximum and minimum Hgb values over the 3 weeks immediately prior to randomization.
5. Mean TSAT ≥ 15% to ≤ 40% over the two most recent consecutive every-other-week measurements prior to randomization of either TSAT or ferritin by ≤10% outside these ranges permitted only if all other inclusion/exclusion criteria are met.
6. Mean serum ferritin ≥ 200 to ≤ 800 µg/L over the two most recent consecutive every other week measurements prior to randomization of either TSAT or ferritin by ≤10% outside these ranges permitted only if all other inclusion/exclusion criteria are met.
7. If being administered epoetin, darbepoetin, or CERA, epoetin dose ≤ 45,000 U/week, darbepoetin dose ≤ 200 µg/week, or CERA dose ≤ 400 µg/month during the four weeks prior to randomization.
8. Minimally adequate measured dialysis dose defined as:
    - For three times weekly dialysis, URR (urea reduction ratio) ≥ 65%, or single-pool Kt/V (dialyzer clearance of urea multiplied by dialysis time, divided by patient's total body water) ≥ 1.2, or $K_{ID}t/V$ (online dialyzer clearance measured using ionic dialysance multiplied by dialysis time, divided by patients total body water) ≥ 1.2, or
    - For four times weekly dialysis, single-pool Kt/V ≥ 0.9.
9. Dialyzer blood flow rate (QB) at the mid-point of dialysis sessions averaged over the 3 to 4 weeks prior to randomization ≥ 250 mL/min.
10. Vascular access for dialysis that will be used upon enrollment with stable function in the judgment of the Investigator without requiring medical or surgical thrombectomy for restoring patency or antibiotics for confirmed infection over the 3 months prior to randomization, and consisting of either a tunneled catheter (internal jugular or subclavian) or an arteriovenous (AV) fistula or graft.
11. Female subjects must be either amenorrheic for ≥ 1 year or agree to not become pregnant by continuous use, during sexual activity, of an effective birth control method acceptable to the Investigator throughout the duration of their participation on study.

12. Patient must be competent and have voluntarily signed the informed consent form.

Exclusion criteria:

1. Patient has living kidney donor identified or living-donor kidney transplant scheduled. (Note: Patients awaiting deceased-donor transplant need not be excluded.)
2. Vascular access for dialysis with femoral catheter or non-tunneled catheter.
3. Received any amount of IV iron during the 4 weeks prior to randomization.
4. If being administered an ESA, change in prescribed dose over the 6 weeks immediatelyprior to randomization.
5. Serum albumin < 3.0 g/dL any time over the 8 weeks prior to randomization.
6. Known cause of anemia other than anemia attributable to renal disease (e.g., sickle celldisease, thalassemia, pure red cell aplasia, hemolytic anemia, myelodysplastic syndrome, etc.).
7. Known active bleeding from any site other than AV fistula or graft (e.g., gastrointestinal, hemorrhoidal, nasal, pulmonary bleeding).
8. Scheduled surgery during the study that may be expected to lead to significant blood loss.
9. RBC or whole blood transfusion during Stage 1.
10. Hospitalization in the previous three months (except for vascular access surgery) that, in the opinion of the Investigator, confers a significant risk of hospitalization during the course of this study.
11. Noncompliance with the protocol during Stage 1 defined as missing ≥ 3 dialysis sessions during the 3 to 4 weeks immediately prior to Stage 2.
12. Evidence of current malignancy involving a site other than skin (except any melanoma, which renders the patient non-eligible).
13. History of drug or alcohol abuse within the last 6 months.
14. Regularly requiring hemodialysis more than four times per week during Stage 1.
15. Pregnancy or intention to become pregnant before completing all study drug treatment.
16. Known ongoing inflammatory disorder (other than CKD), such as systemic lupus erythematosus, rheumatoid arthritis, or other collagen-vascular disease.
17. Any current febrile illness (e.g., oral temperature > 100.4°F, 38°C).
18. Known active bacterial, tuberculosis, fungal, viral, or parasitic infection requiring antimicrobial therapy or anticipated to require anti-microbial therapy during the patient's participation in this study.
19. Occult tuberculosis requiring prophylactic treatment with anti-tubercular drug(s) that overlaps with the patient's participation in this study.
20. Known positive status for hepatitis B surface antigen (hepatitis B testing is not required as part of this protocol).
21. Known human immunodeficiency virus (HIV) infection (HIV testing is not required as part of this protocol).
22. Cirrhosis of the liver based on histological criteria or clinical criteria (i.e., presence of ascites, esophageal varices, spider nevi, or history of hepatic encephalopathy).
23. Hepatitis C infection with ALT and/or AST levels consistently greater than two times the upper limit of normal during the two months prior to randomization.

Study treatment

Stage 1:
During Stage 1 there was no study treatment administered.

Stage 2:
Patients who meet the Stage 2 eligibility criteria were to be randomized in a 1:1 ratio to:

- SFP in dialysate at 2 μM (11 μg iron/dL of dialysate) or
- Placebo (standard dialysate without SFP).

Patients were stratified at randomization by the following factors:

- Baseline Hgb value (Hgb > 11 g/dL vs. Hgb ≤ 11 g/dL, using the average of the three most recent Hgb values preceding randomization), and
- Baseline ESA dose (the weekly dose as of the time of randomization), with patients receiving > 13,000 units/week epoetin (or > 40 μg/week darbepoetin, or > 220 μg/month CERA) randomized separately from patients receiving ≤ 13,000 Units/week epoetin (or ≤ 40 μg/week darbepoetin, or ≤ 220 μg/month CERA).

Stage 3:
During Stage 3, all patients received open-label SFP at 2 μM (11 μg/dL).

The study duration for Stages 2 and Stage 3 combined was intended to be 18 months, regardless of whether the patient was randomized to SFP or placebo in Stage 2.

Study Drug Withholding:
Study drug administration was to be withheld for a minimum of four weeks if any one of the following hematological or iron parameter criteria is met. All laboratory criteria for study drug withholding including Hgb, TSAT, and serum ferritin required confirmation by 2 consecutive values measured at any time within a 2-week period.

- During both Stages 2 and 3:
  - Pre-dialysis TSAT > 50%, OR
  - Serum ferritin > 1,200 μg/L.
- During Stage 3 only:
  - Hgb ≥ 12.5 and< 13.0 g/dL in conjunction with serum ferritin > 500 μg/L, OR
  - Hgb ≥ 13.0 and< 13.5 g/dL in conjunction with serum ferritin > 100 μg/L, OR
  - Hgb ≥ 13.5 g/dL regardless of serum ferritin.

Efficacy evaluation

Primary Endpoint:

- Mean change from baseline in Hgb assessments during the last 8 weeks of the 12-month randomized treatment period, or last one-sixth of the randomized treatment period for patients who prematurely withdraw from study treatment, but will include a minimum of at least the last two Hgb values.

Secondary Endpoints:

- The incidence of "treatment failures," defined as decrease in Hgb to < 9 g/dL sustained for ≥ 2 consecutive weeks.
- The incidence of a decrease in Hgb of ≥ 1.0 g/dL from baseline sustained for ≥ 2 consecutive weeks.
- The incidence of decrease in ferritin to < 100 μg/L sustained for ≥ 2 consecutive weeks.
- The percent of patient maintaining Hgb concentration in the range of ≥ 9.5 to ≤ 11.5 g/dL for ≥80% of time on study.
- The percent of patients maintaining TSAT in the range of TSAT 20-50% for ≥80% of time on study.
- The percent of patients maintaining ferritin in the range of ferritin 200-800 μg/dL for ≥80% of time on study.
- Variability in Hgb.
- The incidence of requiring red blood cell or whole blood transfusion, and IV iron administration (in aggregate and separately).

Exploratory Endpoints:

- The incidence of increase in Hgb to >12 g/dL sustained for ≥ 2 consecutive weeks.
- The incidence of increase in Hgb of ≥ 1.0 g/dL from baseline sustained for ≥ 2 consecutive weeks.
- Time to decrease in Hgb < 9 g/dL or ferritin to < 100 μg/L; to decrease in Hgb of ≥ 1.0 g/dL from baseline; increase in Hgb to >12 g/dL; to increase in Hgb of ≥ 1.0 g/dL from baseline.
- Change in ferritin, TSAT, serum iron and CHr, from baseline to the last 8 weeks (or one sixth) of the randomized treatment period.
- The incidence sustained increase in ESA dose by ≥ 25%
- The change in prescribed ESA dose, and ESA Resistance Index (ERI) and weight adjusted ERI, from baseline to the last 8 weeks (or one-sixth) of the randomized treatment period.
  ERI is defined as (based on prescribed ESA dose):
  ERI = ESA dose (U/wk)/Hgb (g/dL) = U/wk/g/dL and
  The body weight-adjusted ERI is calculated as:
  ERI/kg = ESA dose (U/kg/wk)/Hgb (g/dL) = U/kg/wk/g/dL.

Safety assessment

The studies included the following safety endpoints:

- The incidence of all adverse events (AEs) reported during the study, including the seriousness, severity, and assessed relatedness to study drug.
- Number and percent of patients temporarily or permanently discontinued from study drug treatment due to AEs.
- The number and percent of patients with of AEs of special interest, including:

    - Cardiovascular events (e.g., cerebrovascular accident, nonfatal myocardial infarction, cardiac death),
    - Other venous or arterial thrombotic event s including vascular access thrombosis,
    - Systemic/serious infections (e.g., bacteremia, fungemia, pneumonia, vascular access infection),
    - Intradialytic hypotension,
    - Anaphylactic/anaphylactoid reactions and other hypersensitivity reactions
- Change from baseline in physical examination findings, vital signs, laboratory data, and electrocardiograms (ECGs).
- The change in serum iron, unbound iron binding capacity (UIBC) and TSAT from pre to post dialysis, overall and in subjects with serious adverse events (SAEs).

Definition of Intradialytic Hypotension (IDH) as Adverse Events:

IDH were to be reported as an AE in this study only if the IDH met both of the following definitions:

- Definition of IDH: a systolic blood pressure (SBP) decreased from pre-dialysis baseline by $\geq$ 20 mm Hg that results in a value < 90 mm Hg during dialysis, OR any procedural hypotension that results in premature termination or interruption of dialysis irrespective of the magnitude of decrease in SBP.
- Definition of AE: an untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. IDH observed in a patient on study were not be reported as an AE unless the severity [e.g., magnitude of decrease in blood pressure (BP)] or frequency [e.g., number of IDH events per dialysis session] of the IDH exceeded that patient's established pattern of IDH prior to entering the study.

Each report of an AE of IDH (meeting both above criteria) was to be characterized by the Investigator as (1) symptomatic vs. asymptomatic and (2) requiring intervention vs. not requiring intervention, according to the criteria below.

- Symptomatic IDH if the BP changes were associated with any one or more of the following: abdominal discomfort; yawning; sighing; nausea; vomiting; muscle cramps; restlessness; dizziness or fainting; or anxiety.
- IDH requiring intervention if the BP changes were associated with any one or more of the following interventions: IV saline or other isotonic solution, IV mannitol, low temperature dialysate, terminating or reducing ultrafiltration, or stopping dialysis altogether.

Definition of Anaphylaxis/Anaphylactoid Reactions:

Hypersensitivity reactions, including anaphylaxis/anaphylactoid reactions, were defined as the acute onset (within minutes to one hour after exposure to study drug) of an illness characterized by either or both of the following:

1) Involvement of the skin, mucosal tissue, or both (e.g., generalized hives, pruritus, or flushing; or swollen lips-tongue-uvula), or
2) Thoraco-lumbar back pain not known to be caused by any factor other than possible hypersensitivity reaction,

AND either or both of the following:

a) Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxemia), or
b) Reduced BP or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence).

Possible events of anaphylaxis/anaphylactoid reaction were to be reviewed and assessed by an independent Data Safety Monitoring Board (DSMB) as to whether or not the event was indeed a hypersensitivity reaction and related to study drug using the above proposed definition but subject to modification by the DSMB.

Statistical methods

Sample Size Estimation:

Sample size estimation was based on a comparison of means using a 2-sample t-test with an alpha level of 5% (2-sided). Assuming a common standard deviation of 1.25 g/dL for the change from baseline Hgb, a sample size of 133 patients per treatment group would provide 90% power to detect a treatment difference ≥ 0.5 g/dL in the Hgb change from baseline between SFP and placebo.

A blinded interim analysis was to be performed after approximately 50% of the targeted 300 patients have been randomized to Stage 2 for the purpose of verifying assumptions underlying the sample size calculation to assure adequate power for the primary efficacy endpoint. (This was done and did not result in a sample size change).

Analyzed population:

Efficacy Data Sets
The primary analysis of the primary, secondary and exploratory endpoints were to be based on the intent-to-treat (ITT) population, defined as all patients who are randomized to treatment group in the randomized, controlled treatment period (Stage 2).

A supportive efficacy analysis of the primary efficacy endpoint was to be based on the "efficacy-evaluable" patient population, which is defined as all randomized patients who received study drug and either (1) complete ≥ 36 study drug exposures (expected to be approximately 12 weeks), or (2) are withdrawn from study prior to 36 study drug exposures for a reason of suspected study drug toxicity or Protocol-Mandated Change in Anemia Management and did not have an ESA dose change or receive any IV iron, both of which are prohibited during Stage 2.

Safety Data Set
The safety analysis data set included all patients exposed to any amount of study drug, in either Stage 2 or Stage 3; with the primary analysis of interest being the comparison of safety parameters during the parallel-group Stage 2 period of the study.

Efficacy Analyses:

Primary Efficacy Endpoint:
Formal hypothesis testing of the primary efficacy endpoint (the mean change from baseline in Hgb assessments during the last 8 weeks of the 12-month randomized treatment period, or last one-sixth of the randomized treatment period for patients who prematurely withdraw from study treatment, but will include a minimum of at least the last two Hgb values) was to be based on the comparison of SFP 2 μM (11 μg/dL) vs. placebo, tested with a two-sided 5% significance level.

The change from baseline in Hgb (average value during evaluation period at end of study minus baseline value) during Stage 2 was to be compared between the treatment groups using an analysis of covariance (ANOVA) model. The ACOVA model should include treatment as the main effect, with adjustment for stratification factors used for randomization: baseline Hgb (> 11 g/dL vs. ≤ 11 g/dL) and baseline ESA dose ([> 13,000 units/week epoetin or > 40 μg/week darbepoetin, or > 220 μg/month CERA] vs. [≤ 13,000 units/week epoetin or ≤ 40 μg/week darbepoetin, or ≤ 220 μg/month CERA]). Least-squares means were to be presented for each treatment group.

For the primary analysis, missing Hgb values were not to be imputed or carried forward from previous visits in the derivation of mean values over designated time periods. All observed Hgb values in a given time interval were to be used to calculate the mean value. Further details for handling missing and incomplete data for were to be addressed in the statistical analysis plan.

Secondary and Exploratory Endpoints:
Secondary efficacy endpoints were to be analyzed in a sequential manner with fixed sequences using hierarchical ordering to control alpha at an overall 0.05 level. Once a secondary efficacy endpoint was assessed to be not statistically significant, the remaining efficacy endpoint analyses were to be considered descriptive. Any statistical testing of exploratory endpoints was to be considered for descriptive purposes only. ANOVA should be used as the primary method of analysis for all continuous outcome variables. The Cochran-Mantel-Haenszel chi-square test should be used to evaluate differences between treatment groups in categorical variables. These analyses should control for the randomization stratification variables, as appropriate.

Safety Analyses:
Descriptive analysis was to be performed.

Protocol Amendments:

Protocol amendment 1 (April 20, 2011):
Major changes included:

- The design of Stage 2 of the study was changed from double-blinded to single-blinded (only the study patients are blinded to treatment assignment).
- For entry criteria, the maximal allowable mean ferritin for Stage 2 was increase from 700 to 800 μg/L
- Added a secondary efficacy endpoint: "The percent of patients maintaining Hgb concentration ≥ 10.0 g/dL analyzed at 4-week intervals (e.g., Weeks 1 through 4, 5 through 8, etc.)."
- Expanded the definition of intra-dialytic hypotension (IDH) to also include "any procedural hypotension that results in premature termination or interruption of dialysis irrespective of the magnitude of decrease in systolic blood pressure."
- Transferred responsibility for review of intra-dialytic hypotension (IDH) and anaphylaxis/anaphylactoid reactions events from an adjudication panel to the DSMB.

Protocol amendment 1 (November 8, 2011):
Major changes included:

- Recent changes in ESA dosing guidelines related to safety concerns with higher Hgb levels introduced ESA dose withholding at lower Hgb levels than previously, which has been widely adopted in clinical practice. As a result, several key changes were made to the protocol to enable continued participation in the study:
    - The duration of Stage 1 of the study was changed from 4 to 16 weeks to 1 to 4 weeks. The several-months long run-in Stage 1 was aimed at achieving a stable ESA dose, and it allowed only two ESA dose changes by ≤30% no more frequently than every 4 weeks. Per the new ESA dose labeling, ESA dose adjustments are made more frequently, and ESA dose reduction or withholding is now recommended when Hgb reaches or exceeds 11 g/dL. Therefore, investigators were unable to abide by the original protocol's ESA dosing requirements during Stage 1 given concerns of patient safety, leading to many protocol deviations and discontinuations from the study. Given these changing practices, the prolonged Stage 1 could not achieve its intended objective of a stable ESA dose. As a result of shortening Stage 1 the maximum possible duration of the study changed from 22 ½ months to approximately 20 months.
    - The Hgb threshold levels were changed, in entry criteria as well as in the "Protocol Mandated Changes in Anemia Management":
        - For Stage 1, the Hgb entry criterion was changed from 10.0-12.5 g/dL to 9.5 to 11.5 g/dL.
        - For Stage 2, the Hgb entry criterion was changed from 10.0-12.0 g/dL to 9.5 to 11.5 g/dL.
        - The "Protocol-Mandated Change in Anemia Management" threshold was changed from Hgb < 9.0 g/dL or > 12.5 g/dL to Hgb < 9.0 g/dL or > 12.0 g/dL.
    - The confirmation of high/low Hgb threshold in "Protocol Mandated Changes in Anemia Management" was changed from "over ≥ 1 week confirmed by ≥ 2 consecutive measurements" to "confirmed by a consecutive repeat value obtained

between ≥ 1 day and ≤ 2 weeks after the first value," to allow for clinical judgment regarding urgency of making change in ESA.

- Clarification of criteria for patient withdrawal from study, with addition of a separate section to clarify criteria for transition to Stage 3, and addition of clarifications of protocol deviations that would require patients to be withdrawn from study.
- The study endpoints and statistical analysis section were significantly updated to:
  - simplify the analysis populations and the analyses being performed on the primary efficacy endpoint;
  - simplify and reorganize the list of additional endpoints, creating secondary and exploratory endpoints that can be more readily compared across treatment groups, and moving items to safety endpoints or to statistical section, as appropriate;
  - add intent to perform formal statistical testing on secondary endpoints.
- Following initial 8 weeks of exposure to study drug, vital signs were to continue to be monitored per dialysis clinic routine and clinically significant episodes of hypotension will be as noted as AEs, but vital signs were to be recorded only once per week instead of at every dialysis session to identify intradialytic hypotension programmatically.

3.1.2 Study Results -- Efficacy

3.1.2.1 Assessment of Comparability of Treatment Groups: Demographics, Baseline and Other Characteristics and Disposition

Demographics:

The Study RMTI-SFP-4 randomized 305 patients at Stage 2 from 43 sites in U.S. The Study RMTI-SFP-5 randomized 294 patients from 41 sites in U.S. and 2 sites in Canada. In Study RMTI-SFP-4, the majority of the subjects were male (67.9%) and a majority were white (55.1%). The mean age was 58.3 years (range of 23 to 89 years). Similarly, in Study RMTI-SFP-5, the majority of the subjects were male (59.5%), most were Caucasian (53.1%), and mean age was 58.5 years (range of 20 to 89 years).

The demographic characteristics were similar for the SFP and placebo groups except that there were slightly more patients in the younger age group in the SFP group as compared to the placebo group in both studies and slightly more males and more Caucasians in the placebo group than in the SFP group in Study SFP-5 (see Table below).

Table 1. Demographics in ITT Population

Demographics	**SFP-4**		**SFP-5**	
	SFP (N=152)	**Placebo (N=153)**	**SFP (N=147)**	**Placebo (N=147)**
Age (years)				
Mean (SD)	56.6 (12.6)	59.9 (13.0)	58.1 (12.7)	59.0 (14.4)

<65 years	111 (73.0)	97 (63.4)	102 (69.4)	95 (64.6)
65-74 years	34 (22.4)	35 (22.9)	31 (21.1)	28 (19.0)
≥75 years	7 (4.6)	21 (13.7)	14 (9.5)	24 (16.3)
Gender, n (%)				
Male	102 (67.1)	105 (68.6)	82 (55.8)	93 (63.3)
Female	50 (32.9)	48 (31.4)	65 (44.2)	54 (36.7)
Race, n (%)				
Asian	8 (5.3)	5 (3.3)	8 (5.4)	4 (2.7)
African American	50 (32.9)	48 (31.4)	64 (43.5)	54 (36.7)
Caucasian	84 (55.3)	84 (54.9)	73 (49.7)	83 (56.5)
Other	10 (6.4)	16 (10.4)	2 (1.4)	6 (4.1)

Reviewer's table

Baseline Characteristics:
Baseline hemoglobin and iron parameters

The baseline mean pre-dialysis hemoglobin level was comparable between the SFP and placebo groups in both studies (see Table below). The baseline mean TSAT, serum ferritin and other iron parameters were also similar between the two groups in both studies.

Table 2. Baseline Hemoglobin and Iron Parameters

Hgb and iron parameters	**SFP-4**		**SFP-5**	
	SFP (N = 152) Mean (SD)	**Placebo (N = 153) Mean (SD)**	**SFP (N = 147) Mean (SD)**	**Placebo (N =147) Mean (SD)**
Hemoglobin (g/dL)	10.96 (0.59)	10.91 (0.63)	10.96 (0.61)	10.94 (0.62)
Iron parameters (n)	149	151	143	145
TSAT (%)	28.1 (8.1)	27.1 (7.8)	27.9 (8.2)	28.2 (8.6)
Ferritin (µg/L)	507.7 (194.8)	511.3 (209.7)	513.8 (200.7)	478.8 (201.2)
TIBC (µmol/L)	42.9 (7.4)	42.2 (7.4)	41.8 (6.2)	42.6 (6.9)
UIBC (µmol/L)	30.9 (6.8)	30.8 (6.5)	30.2 (5.8)	30.7 (6.5)
Serum iron (µmol/L)	12.0 (3.9)	11.4 (3.9)	11.6 (3.8)	11.9 (4.0)
Transferrin (g/L)	1.9 (0.3)	1.9 (0.4)	1.9 (0.3)	1.9 (0.3)
Reticulocyte hemoglobin (pg)	32.4 (2.0)	32.6 (2.0)	32.6 (2.2)	32.5 (1.9)

Renal failure and other medical history:

In Study SFP-4, at baseline the mean duration of renal failure in the study population was 5 years and the mean duration of hemodialysis was 4 years with a range of 5 months to 30 years. The most frequent underlying causes of renal failure were hypertension (62.3%) and diabetes mellitus

(53.1%). The types of vascular access included fistula (75%), graft (17%), and Tunneled Catheter (8%). The baseline renal history parameters were similar between the SFP and placebo groups. About 98% of patients received 3 hemodialysis sessions per week and 2% of patients received 4 hemodialysis sessions per week in both groups. The dialysis parameters were similar between the two groups with a mean Kt/V (Dialyzer clearance of urea multiplied by dialysis time, divided by subject's total body water) of 1.68 and a mean URR (urea reduction ratio) of 74%. The history of intradialytic signs and symptoms was similar for the SFP and placebo groups. The most frequent intradialytic signs or symptoms in the SFP and placebo groups were hypotension (69.6% and 66.9%, respectively) and muscle cramps (64.9% and 62.8%, respectively). At baseline, the classes of other medical history reported most frequently were vascular disorders (99.0% of subjects), metabolism and nutrition disorders (98.3%), endocrine disorders (93.7%), renal and urinary disorders (91.7%), and blood and lymphatic system disorders (89.0%). The most frequently reported individual diagnoses were hypertension (97.3%), hyperphosphatemia (81.7%), anemia (70.7%), and secondary hyperparathyroidism (52.7%). There were no significant differences between the SFP and the placebo groups regarding medical history.

Similarly, in Study SFP-5, the baseline renal history parameters were similar between the SFP and placebo groups. The mean time since the initial diagnosis of renal failure was 6.1 years and the mean duration of hemodialysis was about 4.1 years with a range of 5 months to 22 years. The most frequent underlying causes of renal failure were diabetes mellitus (46.3%) and hypertension (43.5%). The types of vascular access included fistula (68%), graft (21%), and Tunneled Catheter (11%). The baseline renal history parameters were similar between the SFP and placebo groups. About 99% of patients received 3 hemodialysis sessions per week and 1% of patients received 4 hemodialysis sessions per week in both groups. The dialysis parameters were similar between the two groups with a mean Kt/V of 1.68 and a mean URR of 74%. The history of intradialytic signs and symptoms was similar for the SFP and placebo groups. The most frequent intradialytic signs or symptoms in the SFP and placebo groups were hypotension (82.4% and 85.2%, respectively) and muscle cramps (71.8% and 81.7%, respectively). The classes of medical history reported most frequently were metabolism and nutrition disorders (98.6%) and vascular disorders (98.6%), followed by renal and urinary disorders (94.8%), endocrine disorders (89.6%), and blood and lymphatic system disorders (86.5%). The most frequently reported individual diagnoses were hypertension (96.2%), renal failure chronic (92.0%), hyperphosphatemia (82.6%), hyperparathyroidism secondary (64.2%), anemia (60.4%), and type 2 diabetes mellitus (52.4%). In both populations, the baseline medical history was similar for the SFP and placebo groups.

History of iron use, ESA and transfusion:

In Study SFP-4, the majority (75%) of subjects received IV iron prior to study, with iron sucrose the most frequently administered type of IV iron (58%), followed by sodium iron gluconate complex (14%). The mean time from the last dose of IV iron to randomization into Stage 2 was 9 weeks. The mean total IV iron administered within the 2 months prior to screening phase of the study was 328 mg elemental iron. There were no significant differences in IV iron administration history between the SFP and placebo groups. Relatively few subjects received

any oral iron within the 2 months prior to screening in the SFP (4 subjects, 2.7%) and placebo (5 subjects, 3.3%) groups. Epoetin alfa was the most commonly prescribed type of ESA at baseline in both the SFP (95.4%) and placebo (88.9%) groups. The mean baseline prescribed ESA dose per administration was similar between the two groups. The majority of the subjects were in Stratum I (≤13,000 equivalent units/week epoetin) in the SFP (81.6%) and placebo (81.0%) groups. About 25% of patients had history of blood transfusion and the mean time since the last transfusion was about 3 years with minimum of 4 months in those patients. There were no significant differences in history of blood transfusion between the SFP and placebo groups.

In Study SFP-5, the majority of subjects received IV iron within the 2 months prior to screening (83.3%), with iron sucrose the most frequently administered type of IV iron (67.3%) followed by sodium iron gluconate complex (9.9%). The mean time from the last dose of IV iron to randomization into Stage 2 was 9 weeks. The mean total IV iron administered within the 2 months prior to screening was 383 mg elemental iron. There were no significant differences in IV iron administration history between the SFP and placebo groups. Relatively few subjects received any oral iron within the 2 months prior to screening in the SFP (2 subjects, 1.4%) and placebo (1 subjects, 0.7%) groups. Similarly, epoetin alfa was the most commonly prescribed type of ESA at baseline in both the SFP (81.6%) and placebo (80.3%) groups. The mean baseline prescribed ESA dose per administration was similar in both groups. The majority of the randomized subjects were in Stratum I (≤13,000 equivalent units/week Epoetin) in the SFP (81.6%) and placebo (81.0%) groups. About 26% of subjects had history of RBC or whole blood transfusion and the mean time since the last transfusion was about 3 years. There were no significant differences in the history of transfusion between the SFP and placebo groups.

Table 3. History of Iron and ESA Use and Blood Transfusion

	SFP-4		SFP-5	
	SFP (N=152)	**Placebo (N=153)**	**SFP (N=147)**	**Placebo (N=147)**
Any IV Iron Within the 2 Months Prior to Study	114 (75.0)	115 (75.2)	120 (81.6)	125 (85.0)
Total iron administered within 2 months prior to study (mg)	328.4 (241.7)	328.6 (239.7)	381.8 (220.2)	384.1 (294.5)
ESA Weekly Dose				
ESA Stratum I	124 (81.6)	124 (81.0)	113 (76.9)	114 (77.6)
ESA Stratum II	28 (18.4)	29 (19.0)	34 (23.1)	33 (22.4)
History of RBC or whole blood transfusions [n (%)]				
Yes	41 (27.0)	35 (22.9)	38 (25.9)	38 (25.9)
No	111 (73.0)	118 (77.1)	109 (74.1)	109 (74.1)

Note: ESA Stratum I: ≤13,000 equivalent units/week epoetin, Stratum II: >13,000 equivalent units/week epoetin)

Hemodialysis parameters during the study:

A summary of hemodialysis sessions during Stage 2 for the MITT population is presented in the Table below. Hemodialysis session parameters were similar for the SFP and placebo groups. More than 95% of patients received dialysis 3 times weekly in both groups for both studies. The

mean duration of dialysis at each dialysis session was about 3 and half hours, which was similar for the SFP group and the placebo group in both studies. The mean mid-point blood flow rate and the mean dialysate flow rate were also similar for the two treatment groups in both studies (see Table below).

Table 4. Hemodialysis Parameters in Randomized Phase of the study

	SFP-4		SFP-5	
Hemodialysis parameters	**SFP**	**Placebo**	**SFP**	**Placebo**
Frequency of dialysis [n (%)]				
3 times weekly	145 (95.4)	149 (97.4)	142 (96.6)	143 (97.3)
4 times weekly	4 (2.6)	2 (1.3)	1 (0.7)	2 (1.4)
Duration of dialysis session (hours)				
N	149	151	143	145
Mean (SD)	3.6 (0.4)	3.5 (0.4)	3.7 (0.4)	3.7 (0.4)
Mid-point blood flow rate (mL/min)				
N	149	151	143	145
Mean (SD)	415.8 (43.0)	414.4 (47.2)	430.3 (54.7)	425.8 (47.5)
Dialysate flow rate (mL/min)				
N	149	151	143	145
Mean (SD)	711.4 (87.3)	702.2 (88.9)	675.8 (101.0)	663.1 (95.9)

Concomitant Medications:
In Study SFP-4, almost all subjects in the SFP (99.3%) and placebo (100%) groups received 1 or more concomitant medications during the study. The percentages of subjects receiving each of the concomitant medications were generally similar for the SFP and placebo groups. The most frequently reported concomitant medications were doxercalciferol (53.7%), acetylsalicylic acid (46.7%), sevelamer carbonate (35.7%), calcium acetate (32.7%), and paricalcitol (32.0%). The numbers and percentages of subjects who received one or more antihypertensive medications were similar in the SFP and placebo groups at baseline (85.9% and 92.1%, respectively) and at the end of study treatment (83.9% and 87.4%, respectively). The mean number of unique antihypertensive medications per subject was 2.8 in the SFP and placebo groups at baseline and at the end of study treatment.

Similarly, in Study SFP-5, all of subjects in the SFP and placebo groups received 1 or more concomitant medications during the study. The percentages of subjects receiving each of the concomitant medications were generally similar for the SFP and placebo groups. The most frequently reported concomitant medications were acetylsalicylic acid (43.1%), paracetamol (41.7%), doxercalciferol (39.2%) and cinacalcet hydrochloride (28.8%), sevelamer carbonate (28.1%), and clonidine (28.1%). The numbers and percentages of subjects who received 1 or more antihypertensive medications were similar in the SFP and placebo groups at baseline (90.2% and 89.7%, respectively) and at the end of study treatment (86.0% and 84.1%, respectively). The mean number of unique antihypertensive medications per subject was same in the SFP and placebo groups at baseline (2.8) and at the end of study treatment (2.7).

Study Treatment, Duration and Compliance:

The number of vials used per patient per session, was not captured in the database but resides in the manual dosing logs in the TMF. The 2.5 gallon bicarbonate container, to which the 5 mL vial of SFP was added, was designed to provide sufficient SFP for a standard 4 hour dialysis treatment. So the vast majority of subjects used only 1 vial/treatment. In the clinical trials, there were 74 subjects who had dialysis times in excess of 4.5 hrs. Of those, only 16 subjects had ≥ 10 hemodialysis sessions lasting 4.5 hours or longer.

A review of the all HD sessions for the above identified subjects with dialysis times greater than 4.5 hours showed that all subjects used only 1 vial of SFP added to the 2.5 gallon bicarbonate concentrate container for all on study treatments. No subjects required more than 1 vial to complete their treatment.

The mean treatment duration was 157.7 days in the SFP group and 164.6 days in the placebo group in study SFP-4 and 161.2 days in the SFP group and 157.9 days in the placebo group in study SFP-5 (see Table below). Slightly fewer than 50% of study patients received study treatment for ≥20 weeks and only about 20% of study patients received study treatment 44-47 weeks in the randomized phase (Stage 2).

Table 5. Treatment Duration in Randomized Phase (Stage 2)

	SFP (N=148)	**Placebo (N=151)**	**SFP (N = 142)**	**Placebo (N = 144)**
Treatment Duration (days)				
Mean (SD)	157.7 (115.42)	164.6 (111.80)	161.2 (111.10)	157.9 (109.76)
Median	125	143	132	135
Min, Max	1, 332	1, 333	1, 332	3, 332
Duration of exposure (n (%))				
≥1 day	148 (100.0)	151 (100.0)	142 (100.0)	144 (100.0)
≥1 week	147 (99.3)	149 (98.7)	141 (99.3)	143 (99.3)
≥2 weeks	140 (94.6)	147 (97.4)	140 (98.6)	140 (97.2)
≥4 weeks	130 (87.8)	137 (90.7)	133 (93.7)	126 (87.5)
≥8 weeks	109 (73.6)	118 (78.1)	117 (82.4)	114 (79.2)
≥12 weeks	90 (60.8)	103 (68.2)	89 (62.7)	96 (66.7)
≥16 weeks	84 (56.8)	87 (57.6)	77 (54.2)	78 (54.2)
≥20 weeks	68 (45.9)	78 (51.7)	67 (47.2)	71 (49.3)
≥24 weeks	62 (41.9)	65 (43.0)	60 (42.3)	63 (43.8)
≥28 weeks	55 (37.2)	57 (37.7)	51 (35.9)	50 (34.7)
≥32 weeks	46 (31.1)	48 (31.8)	42 (29.6)	44 (30.6)
≥36 weeks	41 (27.7)	40 (26.5)	37 (26.1)	36 (25.0)
≥40 weeks	36 (24.3)	35 (23.2)	34 (23.9)	31 (21.5)
44 -47 weeks	30 (20.3)	32 (21.2)	32 (22.5)	24 (16.7)

In Study SFP-4, the total number of subjects with at least 1 dose not administered and the total number of study drug doses not administered was slightly higher in the SFP group (55 subjects and 149 doses, respectively) than in the placebo group (24 subjects and 81 doses, respectively).

The percentage of the total number of study drug doses not administered of the expected total number of hemodialysis sessions was 1.5% in the SFP group and 0.8% in the placebo group.

In Study SFP-4, the reasons for missing doses included pre-dialysis TSAT >50%, serum ferritin >1200 µg/L, investigator discretion, or bacteremia or fungemia or anti-microbial treatment for systemic or serious infection. The percentage of doses of study drug not received due to other reasons was higher in the SFP group (1%, 101 of 10014 doses) than in the placebo group (0.3%, 34 of 10527 doses. The most commonly reported other reason was due to site personnel error which was also higher in the SFP group as compared to the placebo group (28 instances in the SFP group and 4 instances in the placebo group). In the placebo group, the most common of the other reasons was hospitalization (9 instances in the placebo group and 7 instances in the SFP group). Additional other reasons included missed dialysis sessions (e.g., due to subject vacation or reasons other than hospitalization), problems with study drug availability, subject refusal of study drug, withdrawal from the study, subject was being transitioned to Stage 3, dialysis machine or vascular access issues, and Sponsor mandate as part of a corrective action plan due to site non-compliance.

In Study SFP-5, the total number of subjects with at least 1 dose not administered and the total number of study drug doses not administered were also slightly higher in the SFP group (58 subjects and 221 doses, respectively) than in the placebo group (35 subjects and 166 doses, respectively). The percentage of the total number of study drug doses not administered was 2.2% (221/ 9827) in the SFP group and 1.7% (166/9795]) in the placebo group.

The reasons for missing doses included pre-dialysis TSAT >50%, serum ferritin >1200 µg/L, investigator discretion, or bacteremia or fungemia or anti-microbial treatment for systemic or serious infection. The percentage of doses of study drug not received due to other reasons was higher in the SFP group (1.7%, 167 of 9827 doses) than in the placebo group (1.1%, 110 of 9795 doses). The most commonly reported other reason was due to site personnel error (27 in the SFP group and 10 in the placebo group). Additional other reasons included missed doses due to missed dialysis sessions (e.g., due to subject vacation or reasons other than hospitalization), problems with study drug availability, subject refusal of study drug, withdrawal from the study, subject being transitioned to Stage 3, dialysis machine or vascular access issues, and drug held per sponsor request.

The study drug compliance during Stage 2 randomized phase is shown in Table below.

Table 6. Study Treatment Compliance During Randomized Phase

	SFP-4		**SFP-5**	
	SFP	**Placebo**	**SFP**	**Placebo**
Randomized subjects	152	153	147	147
Subjects who received at least 1 dose	149	151	142	144
Subjects with at least 1 dose of study drug not administered	55	24	58	35
Total number of study drug doses not administered per subject				

Mean (SD)	2.7 (3.1)	3.4 (5.8)	3.8 (4.4)	4.7 (8.4)
Total number of study drug doses not administered	149	81	221	166
Reasons study drug dose not administered (number of doses [%])				
Pre-dialysis TSAT >50%	12 (0.1%)	0 (0.0%)	12 (0.1)	0 (0.0)
Serum ferritin >1200 µg/L	0 (0.0%)	15 (0.1%)	0 (0.0)	39 (0.4)
Bacteremia or fungemia or anti-microbial treatment for systemic or serious infection	31 (0.3%)	31 (0.3%)	39 (0.4)	14 (0.1)
Investigator discretion	5 (0.1%)	1 (0.01%)	3 (0.03)	3 (0.03)
Other	101 (1.0%)	34 (0.3)	167 (1.7)	110 (1.1)

Note: Denominator is the total number of HD sessions during the treatment period (from Study Day 1 to the date of the last treatment period visit).

Subject Disposition:

Study SFP-4:
A total of 305 patients with HDD-CKD were randomized, 152 patients to the SFP group and 153 patients to the placebo group. Of the 305 subjects randomized, 300 (149 in the SFP group, 151 in the placebo group) received study drug and 5 patients did not receive any study drug. The reasons for not receiving the study drug included IV iron administration, sponsor's request, and randomization error in the 3 subjects in the SFP group and adverse event and blood transfusion in 2 subjects in the placebo group.

Of the 305 subjects randomized, 54 (17.7%) subjects completed 48 week treatment in Stage 2, 8 (2.6%) subjects died, and 151 (49.5%) subjects who required protocol-mandated change in anemia management were withdrawn from Stage 2 prior to 48 weeks. There were slightly more subjects who required protocol-mandated change in anemia management in the placebo group (53.6%) as compared to the SFP group (45.4%). In the majority of subjects, this was due to a requirement of an ESA dose change (42.8% in SFP and 45.1% in placebo). For 4 (2.6%) subjects in the SFP group compared to 14 (9.2%) subjects in the placebo group change was due to a requirement for IV iron administration.

There were 37 subjects who had ESA dose change and/or received IV iron administration that were not required per protocol-mandated change in anemia management leading to withdrawal prior to 48 weeks (17 [11.2%]) in the SFP group and 20 [13.1%] in the placebo group); most of these subjects also had an ESA dose change as well.

Other reasons for withdrawal included withdrew consent (4.3%), adverse events (3.3%), RBC or whole blood transfusion (2.6%), protocol violations (1.3%), principal investigator decision (1.3%), sponsor's request (0.7%), and lost to follow-up (0.3%). Slightly more patients withdrew from Stage 2 in the SFP group as compared to the placebo group due to withdrawn consent (4.6% vs. 2%, respectively). There more subjects withdrawn due to RBC or blood transfusion in the placebo group as compared to the SFP group (4.6% vs. 0.7%, respectively).

Study SFP-5:

A total of 294 patients with HDD-CKD were randomized into Stage 2 of the study, 147 patients each to the SFP group and to the placebo group. Of the 294 subjects randomized, 288 subjects (143 in the SFP group and 145 in the placebo group) received study drug and 6 patients did not receive any study drug. The reasons for not receiving study treatment were death (1 in the placebo group), physician's decision (1 in the SFP group), withdrawn consent (1 in the SFP group), and randomization errors (2 in the SFP group and 1 in the placebo group).

Of the 294 subjects randomized, 50 (17%) subjects completed 48 weeks treatment in Stage 2, 10 (3.4%) subjects died, and 158 (53.7%) subjects who required protocol-mandated change in anemia management were withdrawn from Stage 2 prior to 48 weeks. There were more subjects who required protocol-mandated change in anemia management in the placebo group (61.2%) as compared to the SFP group (46.3%). In the majority of subjects, withdrawal was due to a requirement of an ESA dose change (44.2% in SFP and 46.9% in placebo). Three (2%) subjects in the SFP group compared to 21 (14.3%) subjects in the placebo group were due to a requirement for IV iron administration.

There were 20 subjects who had ESA dose change and/or received IV iron administration that was not required per protocol-mandated change in anemia management and were withdrawn prior to 48 weeks (14 [9.5%]) in the SFP group and (6 [4.1%]) in the placebo group); most of these subjects also withdrew due to an ESA dose change.

Other reasons included protocol violations (3.7%), RBC or whole blood transfusion (3.4%), adverse events (3.1%), withdrew consent (2.0%), investigator decision (1.4%), sponsor's request (0.7%), Study drug suspended for >12 weeks (0.3%), and other (5.1%).

The following table presents the subject disposition in the SFP-4 and SFP-5 studies.

Table 7. Subject Disposition

	SFP-4		**SFP-5**	
Subject Disposition	**SFP (N=152)**	**Placebo (N=153)**	**SFP (N=147)**	**Placebo (N=147)**
Received at least one dose of study drug	149 (98.0)	151 (98.7)	143 (97.3)	145 (98.6)
Completed 48 weeks treatment	27 (17.8)	27 (17.6)	28 (19.0)	22 (15.0)
Died	5 (3.3)	3 (2.0)	7 (4.8)	3 (2.0)
Protocol-mandated change in anemia management prior to 48 weeks	69 (45.4)	82 (53.6)	68 (46.3)	90 (61.2)
ESA dose change	65 (42.8)	69 (45.1)	65 (44.2)	69 (46.9)
IV iron administration	4 (2.6)	14 (9.2)	3 (2.0)	21 (14.3)
Non-protocol-mandated change in anemia management	17 (11.2)	20 (13.1)	14 (9.5)	6 (4.1)
ESA dose change	13 (8.6)	17 (11.1)	10 (6.8)	5 (3.4)
IV iron administration	6 (3.9)	5 (3.3)	4 (2.7)	1 (0.7)
Withdrew consent	10 (6.6)	3 (2.0)	1 (0.7)	5 (3.4)
Adverse event	5 (3.3)	5 (3.3)	7 (4.8)	2 (1.4)

RBC or whole blood transfusion	1 (0.7)	7 (4.6)	5 (3.4)	5 (3.4)
Protocol violation	3 (2.0)	1 (0.7)	7 (4.8)	4 (2.7)
Principal Investigator decision	3 (2.0)	1 (0.7)	3 (2.0)	1 (0.7)
Sponsor's request	2 (1.3)	0 (0.0)	0 (0.0)	2 (1.4)
Study drug suspended for >12 weeks	0	0	0 (0.0)	1 (0.7)
Lost to follow-up	1 (0.7)	0 (0.0)	0	0
Other	9 (5.9)	4 (2.6)	9 (6.1)	6 (4.1)

In both studies, the protocol-mandated change in anemia management criteria that triggered subjects to be removed from randomized Stage 2 phase prior to 48 weeks included the following:

- Hgb < 9.0 g/dL or > 12.0 g/dL confirmed by a consecutive repeat value obtained between ≥ 1 day and ≤ 2 weeks after the first value (this constituted meeting criteria for a Protocol-Mandated Change in Anemia Management (PMAM) due to a need for an ESA dose change)
- Hgb > 11.5 g/dL over ≥ 1 week confirmed by ≥ 2 consecutive weekly measurements AND an associated increase in Hgb by ≥ 1 g/dL over 4 weeks (this also constituted meeting criteria for a PMAM due to a need for an ESA dose change)
- Ferritin < 100 µg/L over ≥ 1 week confirmed by ≥ 2 consecutive measurements (this constituted meeting criteria for a PMAM due to a need for IV iron)

Additional analysis was performed for final hemoglobin and serum ferritin values for subjects who withdrew prior to 48 weeks due to protocol-mandated change in anemia management. The following table shows the final hemoglobin and ferritin in the randomized phase (Stage 2) in SFP-4 and SFP-5 studies.

Table 8. Subjects Who Met Criteria for Protocol-Mandated Changes in Anemia Management

	SFP-4		**SFP-5**	
	SFP N=152 n (%)	**Placebo N=153 n (%)**	**SFP N=147 n (%)**	**Placebo N=147 n (%)**
Overall (PMAM)	69 (45.4)	82 (53.6)	68 (46.3)	90 (61.2)
Final Hgb > 12.0 g/dL	41 (27.0)	32 (20.9)	32 (21.8)	21 (14.3)
Final Hgb < 9.0 g/dL	17 (11.2)	27 (17.6)	22 (15.0)	34 (23.1)
Final Ferritin < 100 µg/L	5 (3.3)	17 (11.1)	4 (2.7)	23 (15.6)

In Study SFP-4, the majority of subjects with protocol mandated changes in anemia management had final Hgb values > 12.0 g/dL with slightly more patients in the SFP group (27%) as compared to the placebo group (20.9%) that needed ESA dose change. There were more subjects withdrawn with final Hgb values < 9 g/dL in the placebo group as compared to the SFP group (17.6% vs. 11.2%, respectively). There were also more subjects had final serum ferritin level <100 µg/L in the placebo group as compared to the SFP group (11.1% vs. 3.3%, respectively).

For the remaining subjects who were determined to meet criteria for protocol-mandated changes in anemia management by investigator, 6 subjects in the placebo group had final Hgb >11 g/dL with a previous Hgb >11.5 g/dL. In the SFP group, 6 of 7 subjects had final Hgb >11 g/dL with a previous Hgb >12 g/dL and one subject had final Hgb 10.9 g/dL with the previous value of 10.8 g/dL.

Similarly, in Study SFP-5, there were more subjects with protocol-mandated changes withdrawn with the final Hgb values < 9 g/dL in the placebo group as compared to the SFP group (23.1% vs. 15%, respectively) and more subjects withdrawn with the final Hgb values >12 g/dL in the SFP group as compared to the placebo group (21.8% vs. 14.3%, respectively). There were also more subjects who were withdrawn from Stage 2 due to serum ferritin level <100 μg/L in the placebo group as compared to the SFP group (15.6% vs. 2.7%, respectively).

For the remaining subjects who were determined to meet criteria for protocol-mandated changes in anemia management by investigator, all 9 subjects in the placebo group had final Hgb >11 g/dL. Of those, 6 had the previous Hgb value >12 g/dL and 2 had Hgb ≥11.8 g/dL. In the SFP group, all 11 subjects had final Hgb >11 g/dL. Of those, 8 subjects had the previous Hgb value >12 g/dL and 3 subjects had final Hgb >11.5 g/dL.

Twelve randomized subjects were stratified incorrectly (8 subjects who met the criterion for Stratum I were assigned to Stratum II and 4 subjects who met the criterion for Stratum II were assigned to Stratum I). Subjects who were stratified incorrectly were analyzed according to the stratum to which they were assigned.

Protocol Violations/Deviations:
Study SFP-4:

Protocol deviations identified for the randomized subjects are summarized in Table below. The percentages of subjects with the specific protocol violations cited below were similar in the SFP and placebo groups.

Table 9. Protocol Violations/Deviations in SFP-4

Protocol Deviation	**SFP (N=152) n (%)**	**Placebo (N=153) n (%)**	**Total (N=305) n (%)**
Change in ESA product, dose, or route of administration	62 (40.8)	70 (45.8)	132 (43.3)
Developed withdrawal criteria and were not withdrawn	13 (8.6)	12 (7.8)	25 (8.2)
Did not meet inclusion/exclusion criteria during Stage 2	19 (12.5)	15 (9.8)	34 (11.1)
Received excluded concomitant treatment, such as inappropriate IV iron or oral iron	9 (5.9)	10 (6.5)	19 (6.2)
Received less than the intended full amount of study drug exposure at any visit	32 (21.1)	34 (22.2)	66 (21.6)
Received no study drug on a scheduled day of treatment	84 (55.3)	72 (47.1)	156 (51.1)
Received wrong treatment or incorrect dose of study drug	4 (2.6)	2 (1.3)	6 (2.0)
Satisfied criteria for study drug withholding but study drug not withheld	3 (2.0)	0 (0.0)	3 (1.0)

Study SFP-5:
Protocol deviations identified for the randomized subjects are summarized in Table below. The percentages of subjects with the specific protocol violations cited below were similar in the SFP and placebo groups.

Table 10. Protocol Violations/Deviations in SFP-5

Protocol Deviation	**SFP (N=147) n (%)**	**Placebo (N=147) n (%)**	**Total (N=294) n (%)**
Change in ESA product, dose, or route of administration	56 (38.1)	48 (32.7)	104 (35.4)
Developed withdrawal criteria and were not withdrawn	20 (13.6)	14 (9.5)	34 (11.6)
Did not meet inclusion/exclusion criteria	16 (10.9)	18 (12.2)	34 (11.6)
Eligibility	4 (2.7)	11 (7.5)	15 (5.1)
Received excluded concomitant treatment, such as inappropriate IV iron or oral iron	14 (9.5)	14 (9.5)	28 (9.5)
Received less than the intended full amount of study drug exposure at any visit	36 (24.5)	40 (27.2)	76 (25.9)
Received no study drug on a scheduled day of treatment	96 (65.3)	74 (50.3)	170 (57.8)
Received wrong treatment or incorrect dose of study drug	4 (2.7)	6 (4.1)	10 (3.4)
Satisfied criteria for study drug withholding but study drug not withheld	7 (4.8)	5 (3.4)	12 (4.1)

Analyzed populations

The following are definitions of analyzed populations:

- ITT population: All subjects who were randomized to a treatment group in Stage 2.
- MITT population: Randomized subjects who received at least 1 dose of study drug and also had at least 1 post-baseline Hgb value.
- Efficacy-evaluable population: All randomized subjects who either (1) complete ≥36 study drug exposures (expected to be approximately 12 weeks) in Stage 2, or (2) are withdrawn from study prior to 36 study drug exposures in Stage 2 due to suspected study drug toxicity or a protocol-mandated change in anemia management.
- Safety population: Subjects who received any amount of study drug. Subjects receiving an incorrect treatment are summarized as SFP.

The numbers of subjects in analyzed populations for the two studies are shown below.

Table 11. Analyzed Populations

	SFP-4		**SFP-5**	
Subject Disposition	**SFP**	**Placebo**	**SFP**	**Placebo**
Randomized	152	153	147	147
MITT	148 (97.4)	151 (98.7)	142 (96.6)	144 (98.0)
Evaluable	115 (75.7)	121 (79.1)	112 (76.2)	113 (76.9)

Safety	149 (98.0)	151 (98.7)	143 (97.3)	145 8.6)

3.1.2.2 Analysis of Primary Endpoint(s)

Primary efficacy endpoint

The primary efficacy endpoint was the mean change in Hgb from baseline to end of the treatment (EoT). The Hgb values at EoT were based on all available values obtained during the last 1/6th of each subject's participation in the study regardless of the time or reason subjects were withdrawn or completed randomized, controlled phase (Stage 2) of the study.

ITT Population

The mean changes in hemoglobin from baseline to EoT in the ITT population in the two groups in both studies are presented in Table below. In Study SFP-4, the mean hemoglobin decreased 0.03 g/dL from baseline in the SFP group as compared to 0.38 g/dL in the placebo group. In Study SFP-5, the mean hemoglobin decreased 0.08 g/dL in the SFP group as compared to 0.44 g/dL in the placebo group. The primary efficacy analysis used an ANCOVA model with baseline Hgb as a covariate. The treatment differences in hemoglobin between the SFP and the placebo groups in both studies showed an LS mean difference of 0.35 g/dL and were statistically significant (p =0.01) in both studies.

Table 12. Primary Efficacy Endpoint in ITT population

	SFP-4		**SFP-5**	
	SFP (N = 152)	**Placebo (N = 153)**	**SFP (N = 147)**	**Placebo (N = 147)**
Baseline Hgb (g/dL) Mean (SD)	10.96 (0.59)	10.91 (0.63)	10.96 (0.61)	10.94 (0.62)
EoT Hgb (g/dL), Mean (SD)	10.93 (1.24)	10.53 (1.35)	10.87 (1.36)	10.50 (1.32)
Change in Hgb from Baseline to EOT (g/dL) Mean (SD)	-0.03 (1.15)	-0.38 (1.24)	-0.08 (1.15)	-0.44 (1.16)
ANCOVA analysis with baseline Hgb as the covariate				
LS Mean (SE)	0.06 (0.11)	-0.30 (0.11)	-0.04 (0.11)	-0.39 (0.11)
95% CI of LS Mean	(-0.16, 0.28)	(-0.52, -0.08)	(-0.25, 0.16)	(-0.60, -0.19)
LS Mean Difference (SE)	0.35 (0.14)		0.35 (0.14)	
95% CI of LS Mean Difference	(0.9, 6.2)		(0.8, 6.1)	
P-value	0.010		0.011	

Note: LS Mean (SE) and p-value are from an ANCOVA model with baseline Hgb as the covariate. The model also includes an indicator variable for the baseline ESA dose stratum.
Reviewer's table

MITT population

The primary efficacy endpoint results in MITT population were similar to the results that were obtained from the ITT analysis (see Table below). In Study SFP-4, the mean hemoglobin decreased 0.04 g/dL in the SFP group as compared to 0.39 g/dL in the placebo group. Similarly, in Study SFP-5 the mean hemoglobin decreased 0.09 g/dL in the SFP group as compared to 0.45 g/dL in the placebo group. ANCOVA analysis with baseline Hgb as the covariate showed a treatment difference of LS mean difference of 0.36 g/dL in hemoglobin in both studies. The difference between the SFP and the placebo group was statistically significant (p =0.01) in both studies.

Table 13. Primary Efficacy Endpoint in MITT population

	SFP-4		**SFP-5**	
	SFP (N = 148)	**Placebo (N = 151)**	**SFP (N = 142)**	**Placebo (N = 144)**
Baseline Hgb (g/dL) Mean (SD)	10.96 (0.59)	10.91 (0.63)	10.96 (0.61)	10.93 (0.63)
EoT Hgb (g/dL), Mean (SD)	10.91 (1.25)	10.52 (1.37)	10.87 (1.38)	10.49 (1.33)
Change in Hgb from Baseline to EOT (g/dL) Mean (SD)	-0.04 (1.17)	-0.39 (1.25)	-0.09 (1.18)	-0.45 (1.17)
ANCOVA analysis with baseline Hgb as the covariate				
LS Mean (SE)	0.06 (0.12)	-0.30 (0.11)	-0.05 (0.11)	-0.40 (0.11)
95% CI of LS Mean	(-0.17, 0.28)	(-0.53, -0.08)	(-0.26, 0.17)	(-0.62, -0.19)
LS Mean Difference (SE)	0.36 (0.14)		0.36 (0.14)	
95% CI of LS Mean Difference	(0.08, 0.63)		(0.08, 0.63)	
p-value	0.011		0.011	

Note: LS Mean (SE) and p-value are from an ANCOVA model with baseline Hgb as the covariate. The model also includes an indicator variable for the baseline ESA dose stratum.

Evaluable population

In the efficacy-evaluable population, the mean hemoglobin decreased 0.03 g/dL in the SFP group as compared to 0.35 g/dL in the placebo group in Study SFP-4 (see Table below). Similarly, the mean hemoglobin decreased 0.11 g/dL in the SFP group as compared to 0.44 g/dL in the placebo group in Study SFP-5. ANCOVA analysis with baseline Hgb as the covariate showed that the treatment difference in hemoglobin between the SFP and the placebo group with an LS mean difference of 0.32 g/dL in Study SFP-4 and 0.34g/dL in Study SFP-5. The difference between two treatment groups was borderline statistically significant (p =0.056) in Study SFP-4 and remained to be statistically significant in the Study SFP-5 (p=0.039).

Table 14. Primary Efficacy Endpoint in Evaluable Population

	SFP-4		**SFP-5**	
	SFP (N = 115)	**Placebo (N = 121)**	**SFP (N = 112)**	**Placebo (N = 123)**

Baseline Hgb (g/dL) Mean (SD)	11.01 (0.57)	10.96 (0.64)	10.94 (0.55)	10.92 (0.62)
EoT Hgb (g/dL), Mean (SD)	10.98 (1.33)	10.60 (1.41)	10.84 (1.41)	10.48 (1.38)
Change in Hgb from Baseline to EOT (g/dL) Mean (SD)	-0.03 (1.27)	-0.35 (1.30)	-0.11 (1.25)	-0.44 (1.22)
ANCOVA analysis with baseline Hgb as the covariate				
LS Mean (SE)	0.09 (0.13)	-0.23 (0.14)	-0.05 (0.13)	-0.39 (0.13)
95% CI of LS Mean	(-0.17, 0.36)	(-0.49, -0.04)	(-0.31, 0.16)	(-0.64, -0.14)
LS Mean Difference (SE)	0.32 (0.17)		0.34 (0.16)	
95% CI of LS Mean Difference	(-0.01, 0.65)		(0.02, 0.65)	
P-value	0.056		0.039	

Note: LS Mean (SE) and p-value are from an ANCOVA model with baseline Hgb as the covariate. The model also includes an indicator variable for the baseline ESA dose stratum.

3.1.2.3 Analysis of Secondary Endpoints(s)

Changes in Reticulocyte Hgb Content (CHr), Serum Ferritin, UIBC, serum iron, and TSAT from baseline to the End-of-Treatment (EoT)

The mean changes from baseline to EoT in CHr, ferritin, UIBC, serum iron, and TSAT in SFP-4 and SFP-5 are presented in Table below.

In the two studies, CHr and serum ferritin at EoT decreased less from baseline in the SFP groups than in the placebo groups. There was a smaller mean increase in pre-dialysis UIBC from baseline to EoT in the SFP groups as compared to the placebo groups. The pre-dialysis serum iron and TSAT at EoT decreased less from baseline in the SFP groups than in the placebo groups in both studies. The results in iron parameters and reticulocyte hemoglobin content were consistent with the primary efficacy results in the two studies.

Table 15. Mean change in Reticulocyte Hemoglobin Content and Iron Parameters from Baseline to the End of Treatment

	SFP-4		**SFP-5**	
	SFP N=142 Mean (SD)	**Placebo N=148 Mean (SD)**	**SFP N=140 Mean (SD)**	**Placebo N=141 Mean (SD)**
Reticulocyte Hgb Content (pg)	-0.23 (1.20)*	-0.91 (1.41)	-0.56 (1.46)*	-0.86 (1.48)
Serum Ferritin (µg/L)	-72.3 (133.4)*	-143.1 (188.3)	-67.1 (164.4)*	-122.7 (269.7)
Pre-dialysis UIBC (µmol/L)	1.93 (13.27)*	2.14 (4.45)	0.92 (4.36)*	2.56 (4.65)
Pre-dialysis serum iron (µmol/L)	-0.20 (4.75)	-1.05 (3.66)	-0.24 (3.42)*	-1.34 (3.40)
Pre-dialysis TSAT (%)	-1.1 (9.2)	-3.0 (7.7)	-0.9 (7.7)*	-3.7 (7.3)

Note: UIBC =unsaturated iron binding capacity, TSAT =transferrin saturation
*$p<0.05$ for difference between SFP and placebo.

Change in iron parameters from pre-dialysis to post-dialysis over the course of the treatment period

The mean changes from pre-dialysis to post-dialysis over the course of the treatment period in serum iron, UIBC, and TSAT are shown in Table below. There were mean increases in serum iron, TSAT from pre-dialysis to post-dialysis in the SFP groups as compared to minimal changes in the placebo groups in both studies. On the other hand, there was a decrease in UIBC in the SFP groups as compared to small increase in UIBC in the placebo groups in both studies. These results were consistent with the primary efficacy results.

Table 16. Change from Pre-dialysis to Post-dialysis in Iron Parameters during the Treatment Period

	SFP-4		**SFP-5**	
	SFP N=142 Mean (SD)	**Placebo N=147 Mean (SD)**	**SFP N=139 Mean (SD)**	**Placebo N=141 Mean (SD)**
Serum iron (µmol/L)	17.45 (8.70)	0.63 (3.08)	19.68 (6.82)	1.19 (3.47)
TSAT (%)	32.7 (15.8)	-0.4 (6.9)	37.5 (11.5)	0.1 (6.9)
UIBC (µmol/L)	-11.96 (6.60)	2.38 (3.25)	-13.31 (5.02)	2.57 (3.35)

Note: TSAT =transferrin saturation, UIBC =unsaturated iron binding capacity

Subpopulations

Pooled analyses of efficacy data from SFP-4 and SFP-5 studies by subgroup were performed to explore whether the treatment effect differed among the following subgroups of clinical interest.

*Age:*There were higher percentages of subjects <65 years of age (72.1% and 63.7%) than subjects ≥65 years of age (27.9% and 36.3%) in both treatment groups (SFP and placebo groups, respectively). In both the <65 year-old subjects and the ≥65 year-old subjects, the SFP group had a smaller mean decrease from baseline (-0.3 g/L and -1.3 g/L, respectively) in Hgb than the placebo group (-3.0 g/L and -6.2 g/L, respectively). The results in both age groups were consistent with overall study results.

*Gender:*There were higher percentages of male subjects (61.0% and 66.1%) than female subjects (39.0% and 33.9%) in both treatment groups. In both the male and female subgroups, the SFP group had a smaller mean decrease from baseline (-0.5 g/L and -0.7 g/L, respectively) in Hgb than the placebo group (-3.5 g/L and -5.4 g/L, respectively). The results in both gender groups were consistent with overall study results.

Race: Similar percentages of subjects were white (52.8% and 55.9%) and nonwhite (47.2% and 44.1%) in the SFP and placebo groups, respectively. In both the white and nonwhite subgroups, the SFP group had a smaller mean decrease from baseline (-0.8 g/L and -0.4 g/L, respectively) in Hgb than the placebo group (-4.8 g/L and -3.4 g/L, respectively). The results in both race groups were consistent with overall study results.

HD parameters: Change in Hgb from baseline to the end-of-treatment in subgroups based on HD parameters is shown in the Table below.

Table 17. Change from baseline at EoT in Hemoglobin (g/L) by HD Parameters

HD parameters		**SFP**	**Placebo**
Type of vascular access			
Catheter	n	28	30
	Mean (SD)	0.1 (11.71)	-5.2 (13.61)
Graft/fistula	n	260	263
	Mean (SD)	-0.7 (11.71)	-4.1 (11.95)
Dialysis flow rate			
≤600 mL/min	n	111	128
	Mean (SD)	-1.0 (12.35)	-5.6 (11.31)
>600 mL/min	n	177	165
	Mean (SD)	-0.4 (11.29)	-3.1 (12.63)
Blood flow rate			
≤400 mL	n	141	145
	Mean (SD)	-0.2 (11.83)	-5.7 (11.94)
>400 mL/min	n	147	148
	Mean (SD)	-1.0 (11.59)	-2.6 (12.12)
Dialysis adequacy			
Kt/V ≤1.6	n	110	126
	Mean (SD)	-2.0 (12.43)	-2.6 (12.24)
Kt/V >1.6	n	130	119
	Mean (SD)	1.3 (11.15)	-4.7 (12.35)
Type of dialyzer membrane			
Cellulose triacetate	n	11	13
	Mean (SD)	-6.6 (11.08)	-5.0 (7.48)
Polyamide	n	8	59
	Mean (SD)	-0.7 (11.05)	-1.4 (12.20)
Polysulfone	n	184	161
	Mean (SD)	-0.9 (12.03)	-5.7 (12.12)
Polyarylethersulfone	n	45	58

	Mean (SD)	1.9 (10.81)	-2.2 (12.39)
Dialyzer reuse			
Yes	n	74	95
	Mean (SD)	-1.5 (11.78)	-3.3 (12.69)
No	n	214	198
	Mean (SD)	-0.3 (11.68)	-4.6 (11.84)

Type of vascular access: Most subjects (90.1%) used the graft/fistula type of vascular access in the study. In both the graft/fistula vascular access subgroup and the catheter vascular access subgroup, the SFP group had a smaller change from baseline (-0.7 g/L and 0.1 g/L, respectively) in Hgb than the placebo group (−4.1 g/L and -5.2 g/L, respectively).

Dialysate flow rate: There was a slightly higher percentage of subjects with a >600 mL/m in dialysate flow rate at baseline (58.6%) than with a ≤600 mL/min dialysate flow rate at baseline (41.4%) in the studies. In both the dialysate flow rate ≤600 mL/min subgroup and the >600 mL/min subgroup, the SFP group had a smaller mean decrease from baseline (-1.0 g/L and -0.4 g/L, respectively) in Hgb than the placebo group (-5.6 g/L and -3.1 g/L, respectively).

Blood flow rate: In the blood flow rate ≤400 mL/min subgroup the SFP group had a smaller decrease from baseline in Hgb (-0.2 g/L) than the placebo group (-5.7 g/L). In the higher blood flow rate (>400 mL/min) subgroup, the SFP group also had a mean decrease in Hgb (−1.0 g/L) as compared with placebo group (-2.6 g/L), but the difference was smaller.

Dialysis adequacy: In the higher measured dialysis adequacy (Kt/V>1.6) subgroup the SFP group had an increase from baseline in Hgb (1.3 g/L) while the placebo group had a decrease in Hgb from baseline (-4.7 g/L). On the other hand, in the lower measured dialysis adequacy (Kt/V ≤1.6) subgroup, the SFP group had a similar decrease in Hgb from baseline (-2.0 g/L) compared with placebo group (-2.6 g/L).

Type of dialyzer membrane: For both the SFP and placebo groups, the majority patients used the polysulfone dialyzer membrane at baseline (59.7%). In those using polysulfone dialyzer membrane, the SFP group had a smaller mean decrease from baseline in Hgb (-0.9 g/L) than in the placebo group (-5.7 g/L). In those using polyarylethersulfone dialyzer membrane subgroup (about 17.6% of patients), Hgb showed an increase from baseline in the SFP group (1.9 g/L) and a decrease from baseline in the placebo group (-2.2 g/L). In those using polyamide dialyzer membrane subgroup, the SFP group had a small mean decrease from baseline in Hgb (-0.7 g/L) compared with the placebo group (-1.4 g/L). On the other hand, in those using the cellulose triacetate dialyzer membrane type subgroups, the SFP group had a more decrease from baseline in Hgb (-6.6 g/L) compared with the placebo group (-5.0 g/L); however, there were few patients in this subgroup (total=24)..

Dialyzer reuse: The majority (70.8%) of patients had no dialyzer reuse at baseline. In the subgroup with no dialyzer reuse at baseline, the SFP group had a smaller mean decrease from baseline in Hgb (-0.3 g/L) than the placebo group (-4.6 g/L). In the subgroup with dialyzer reuse

at baseline, the difference between the SFP group and the placebo group was smaller (-1.5 g/L and -3.3 g/L, respectively).

3.2 Phase 2 Study NIH-FP-01

Study NIH-FP-01 was submitted to support labeling "To reduce the prescribed dose of erythropoiesis stimulating agent (ESA) required to maintain desired hemoglobin levels."

3.2.1 Study Protocol

Study title: Physiological Iron Maintenance in ESRD Subjects by Delivery of Soluble Ferric Pyrophosphate (SFP) via Hemodialysate: The PRIME Study

Study Design

This was a multicenter, randomized, placebo-controlled, double-blinded, phase 2 trial to evaluate the safety and efficacy of SFP via hemodialysate in patients with HDD-CKD.

Study population

Inclusion Criteria:

1. Male and female subjects ≥ 18 years of age.
2. End-stage renal disease undergoing maintenance hemodialysis 3 to 4 times a week for at least 4 months and expected to remain on this schedule and be able to complete the study. Subjects on a cadaveric transplant list need not be excluded for this reason unless there is an identified donor.
3. Mean Hgb in the range of ≥ 9.5 to ≤ 12.0 g/dL during screening
4. The difference between the maximum and minimum Hgb values during screening does not exceed 1.0 g/dL.
5. Mean ferritin ≥ 200 to ≤ 1000 µg/L during screening.
6. Mean TSAT ≥ 15% to ≤ 40% during screening (Excursion of TSAT by ≤10% outside this range permitted only if all other inclusion/exclusion criteria are met).
7. Any and all serum albumin measured during the 2 months preceding randomization must be ≥ 3.0 g/dL.
8. Prescribed ESA dosing remaining in the range of ≥ 4,000 to ≤ 45,000 U/week epoetin or ≥ 12.5 to ≤ 200 µg/week darbepoetin during the 6 weeks preceding randomization.
9. Required IV iron at any time in the 6 months preceding randomization.
10. Female subjects must be either amenorrheic for a minimum of 1 year or agree to not become pregnant by continuous use, during sexual activity, of an effective birth control method acceptable to the Investigator throughout the duration of their participation on study.
11. Minimally adequate measured dialysis dose defined as:

   i. For 3 times weekly dialysis, URR (urea reduction ratio) > 65% or single-pool Kt/V (dialyzer clearance of urea multiplied by dialysis time, divided by patient's total body water) > 1.2, or
   ii. For 4 times weekly dialysis, single-pool Kt/V > 0.9.
12. Dialyzer blood flow rate (QB) at the mid-point of dialysis sessions averaged over the
13. 4 weeks prior to randomization ≥ 225 mL/min.
14. Undergoing dialysis only using an arteriovenous (AV) fistula or graft.
15. Must be willing and able to provide written informed consent directly or through their authorized representative.

Exclusion Criteria:

1. Vascular access for dialysis is a catheter.
2. During the 6 months prior to randomization, infection of the vascular access to be used at the time of randomization.
3. Received a total of > 600 mg IV iron during the 6 weeks prior to randomization.
4. Received any amount of IV or oral iron during the 2 weeks prior to randomization.
5. Change in prescribed ESA dose:
   a. Any change in prescribed ESA dose within 4 weeks prior to randomization.
   b. The prescribed ESA dose at the time of randomization is > 25% higher or lower than the prescribed dose at 6 weeks prior to randomization.
   c. Change in prescribed type of ESA (e.g., epoetin vs. darbepoetin) or route of administration within 6 weeks prior to randomization.
6. Actual ESA dosing missed or withheld for a cumulative total of ≥ 1 week for any reason during the 6 weeks prior to randomization.
7. Known cause of anemia other than anemia attributable to renal disease (e.g., sickle cell disease, thalassemia, pure red cell aplasia, hemolytic anemia, myelodysplastic syndrome, etc.).
8. Known active bleeding from any site other than AV fistula or graft (e.g., gastrointestinal, hemorrhoidal, nasal, pulmonary bleeding).
9. Known coagulation disorder.
10. Scheduled surgery during the study that may be expected to lead to significant blood loss.
11. RBC or whole blood transfusion within 12 weeks prior to randomization.
12. Scheduled kidney transplant or a donor has been identified but the transplant has not been scheduled.
13. Known ongoing inflammatory disorder (other than CKD), such as systemic lupus erythematosus, rheumatoid arthritis, other collagen-vascular diseases, etc.
14. Hospitalization in the previous 3 months (except for vascular access surgery) that, in the opinion of the Investigator, confers a significant risk of hospitalization during the course of this study.
15. Evidence of current malignancy involving sites other than skin (except any melanoma, which renders the patient non-eligible).
16. History of drug or alcohol abuse within the last 6 months.
17. Regularly requiring hemodialysis more than 4 times per week.
18. Known to be pregnant or breast-feeding at screening.
19. Any febrile illness (e.g., oral temperature > 100.4°F, 38°C) during screening.

20. Known active tuberculosis, fungal, viral, or parasitic infection requiring anti- microbial therapy or anticipated to require anti-microbial therapy during the patient's participation in this study. Subjects with hepatitis C, in the absence of cirrhosis, are not excluded from participation in the study if ALT and AST levels are below 2 times the upper limit of normal on a consistent basis during the 2 months preceding randomization.
21. Occult tuberculosis requiring prophylactic treatment with anti-tubercular drug(s) that overlaps with the patient's participation in this study.
22. Known positive status for hepatitis B surface antigen (hepatitis B testing is not required as part of this protocol).
23. Known human immunodeficiency virus (HIV) infection (HIV testing is not required as part of this protocol).
24. Cirrhosis of the liver based on histological criteria or clinical criteria (e.g., presence of ascites, esophageal varices, spider nevi, or history of hepatic encephalopathy).
25. Hepatitis C infection if ALT and/or AST levels are consistently greater than twice the upper limit of normal at any time during the 2 months prior to randomization.
26. Participated in another clinical trial of an investigational drug or device within 30 days prior to randomization in this trial.
27. Subjects who are anticipated to be unable to complete the entire study (e.g., due to a concurrent disease).

Study Treatment

Subjects were randomized in a 1:1 ratio to receive SFP-containing dialysate or control iron free dialysate (placebo) at every dialysis session.

SFP dose: approximately 2 μM (11 μg /dL) of iron in final dialysate solution.
Placebo control solution: iron-free liquid bicarbonate concentrate.

The total treatment duration of the study was 36 weeks plus a 1-week follow-up after the last study drug treatment.

Oral or IV iron and ESA use:
Oral iron treatment was prohibited for a total of 2 weeks prior to anticipated randomization and for the entire duration of the study.

During Week 1 through Week 4, IV iron was prohibited; and changes in ESA dose, type of ESA (e.g., epoetin vs. darbepoetin), and route of administration were prohibited except where ESA dose reduction was needed to manage high Hgb levels.

Beginning at Week 5, IV iron could be administered and the ESA dose could be adjusted. The administration of IV iron and adjustment of ESA dose were based on a pre-specified algorithms, with the goal of maintaining Hgb in the target range of 9.5 to 11.5 g/dL.

Study drug administration was to be withheld in 2-week blocks of time for any one of the following:

- Pre-dialysis TSAT >50% confirmed by a consecutive repeat value any time ≥1 day and ≤2 weeks after the first value, OR
- Serum ferritin >1,200 µg/L confirmed by a consecutive repeat value any time ≥1 day and ≤2 weeks after the first value, provided that high-sensitivity C-reactive protein (hs-CRP) had not simultaneously increased by ≥100% from the subject's baseline hs-CRP level, OR
- Hgb ≥13.0 g/dL confirmed by a consecutive repeat value any time ≥ 1 day and ≤2 weeks after the first value, provided that the subject had been off all ESA for ≥ 4 weeks at the time of the confirming Hgb value.

Efficacy Endpoints

Primary Endpoints

1. Efficacy Endpoint: The percent change from baseline in ESA dose required to maintain Hgb in the target range, adjusted for Hgb.
2. Safety Endpoints: Safety and tolerability will be determined by clinically significant changes in physical examinations and vital signs, clinical laboratory measures, and incidence and severity of adverse events.

Secondary Efficacy Endpoints

1. The incidence of "patient responders," defined as ≥ 25% decrease from baseline in ESA dose sustained continuously for ≥ 8 weeks and the incidence of "patient failures," defined as ≥ 25% increase from baseline in ESA dose sustained continuously for ≥ 8 weeks
2. The amount of supplemental IV iron needed.
3. Maintenance of hemoglobin in the range of 9.5 to 11.5 g/dL.
4. Variability in hemoglobin [Hgb-var].
5. Iron delivery to the erythron as estimated by hemoglobin generation in response to erythropoietin (ESA response index, or ERI, calculated as ESA dose/Hgb). The ERI was to be divided by body weight in kilograms to obtain a modified ERI (ERI/kg).
6. Markers of inflammation and oxidative stress.

Safety Assessment

Safety and tolerability of the drug were determined by the incidence and severity of AEs, clinical laboratory measures, and clinically significant changes in physical examinations and vital signs.

Statistical Methods

The protocol stated that this clinical trial was exploratory in nature. Statistical tests were considered to be descriptive rather than conclusive and were not be adjusted for multiple comparisons. All tests were to be two-sided. The sample size of approximately 50 patients per treatment group (100 patients combined for the two groups, not including the 11 patients enrolled prior to protocol version 34) was considered adequate for the intended purposes of this trial.

3.2.2 Study Results -- Efficacy

3.2.2.1 Assessment of Comparability Treatment Groups: Demographics, Baseline and Other Characteristics and Disposition

Demographics

In Study NIH-FP-01, the majority of the subjects were male (61.2%) and most were white (61.2%). Mean age was 59.0 years (range of 25 to 93 years). There were slightly more males and more Caucasians in the placebo group than in the SFP group (see Table below).

Table 18. Demographics in NIH-FP-01 in Safety Population

	SFP (N=54)	Placebo (N=49)	Total (N=103)
Age (years)			
Mean (SD)	59.4 (12.40)	58.5 (13.89)	59.0 (13.07)
Median	59.0	58.0	59.0
Min, Max	37, 93	25, 86	25, 93
Gender, n (%)			
Male	31 (57.4)	32 (65.3)	63 (61.2)
Female	23 (42.6)	17 (34.7)	40 (38.8)
Race, n (%)			
Asian	1 (1.9)	0	1 (1.0)
Black or African American	22 (40.7)	17 (34.7)	39 (37.9)
White	31 (57.4)	32 (65.3)	63 (61.2)

Baseline Characteristics

Baseline hemoglobin and iron parameters

The baseline mean pre-dialysis hemoglobin level was comparable between the SFP and placebo groups (see Table below). The baseline mean TSAT and other iron parameters were also similar between the two groups.

Table 19. Baseline hemoglobin and iron parameters in MITT population

	SFP N=52 Mean (SD)	**Placebo N=51 Mean (SD)**
Hemoglobin (g/dL)	10.96 (0.72)	11.11 (6.87)
Iron parameters		
TSAT (%)	26.7 (7.07)	28.4 (7.54)
TIBC (µmol/L)	45.72 (6.68)	46.1 (7.83)
UIBC (µmol/L)	40.77 (5.51)	41.21 (6.81)
Serum iron (µmol/L)	11.96 (3.03)	13.01 (4.10)

Reticulocyte hemoglobin content (pg)	32.76 (1.84)	32.49 (2.17)

Renal history and other medical history:

The baseline renal history parameters were similar for the SFP and placebo groups. At baseline the mean time since the initial diagnosis of renal failure was 5.1 years. At baseline the mean time since current vascular access started was 2.6 years, and 42.7% of subjects had a history of angioplasty for the current vascular access. All patients received 3 times hemodialysis per week except one patient who received 4 times per week in the placebo group.

The baseline medical history was similar for the SFP and placebo groups. The classes of medical history reported most frequently were vascular disorders (100% of subjects), renal and urinary disorders (99.0%), metabolism and nutrition disorders (98.1%), endocrine disorders (89.3%), and blood and lymphatic system disorders (86.4%). The most frequently reported individual diagnoses were hypertension (95.1%), renal failure chronic (95.1%), hyperphosphatemia (66.0%), procedural hypotension (62.1%), and hyperparathyroidism secondary (60.2%).

Baseline IV iron and ESA use:

The mean times at baseline since the last IV iron therapy and the last oral iron therapy were 9.9 weeks and 37.5 weeks, respectively, with a mean of 99.4 mg of total IV iron administered in the last 6 weeks prior to randomization.

Almost all subjects (101 of 103 subjects) received epoetin for their prescribed ESA dose, with the mean dose being 9412.2 U/week. The majority of patients were in Stratum I (≤13,000 equivalent units/week epoetin: 80 subjects, 77.7%). The mean prescribed ESA dose in equivalent units of epoetin was 9345.9 U/week for the 103 subjects in the safety population, 7191.6 U/week for the 80 subjects in Stratum I, and 16839.1 U/week for the 23 subjects in Stratum II.

Table 20. History of Iron and ESA use and Blood Transfusion

	SFP (N=54)	**Placebo (N=49)**
Any IV Iron Within the 6 weeks prior to study, n (%)	53 (98)	45 (100)
Total iron administered 6 weeks prior to randomization (mg) Mean (SD)	102.1 (128.6)	96.4 (111.9)
Prescribed ESA dose - equivalent units of epoetin (U/week)		
Mean (SD)	9483.2 (5413.86)	9205.9 (5500.05)
ESA Stratum I, n (%)	41 (75.9)	39 (79.6)
ESA Stratum II, n (%)	28 (18.4)	29 (19.0)
History of RBC or whole blood transfusions, n (%)	13 (24.1)	10 (20.4)
Yes	21 (38.9)	20 (40.8)
No	33 (61.1)	29 (59.2)

ESA Stratum I: ≤13,000 equivalent units/week epoetin, Stratum II: >13,000 equivalent units/week epoetin)

Concomitant Medications:

All subjects in both groups received one or more concomitant medications during the study. The percentages of subjects receiving concomitant medications were similar for the SFP and placebo groups. The most frequently reported concomitant medications were paricalcitol (60.2%) given for calcium homeostasis, paracetamol (57.3%) given as an analgesic, influenza vaccine (51.5%), sodium chloride (48.5%) given as an IV additive, calcium acetate (48.5%) for treatment of hyperkalemia and hyperphosphatemia, and sevelamer carbonate (48.5%) also given for treatment of hyperkalemia and hyperphosphatemia.

Study Treatment Compliance

The mean duration of exposure to study drug was 212 days (SD=76.1) and 222 days (SD=58.1) in the SFP and placebo groups, respectively (see Table below). The majority of subjects received ≥32 weeks but less than 36 weeks of treatment in the SFP (79%) and placebo groups (80%).

Table 21. Treatment Duration in Randomized Phase in MITT population

	SFP (N=52)	**Placebo (N=51)**
Treatment Duration (days) exposure		
Mean (SD)	212.1 (76.08)	222.1 (58.12)
Min, Max	1, 249	1, 249
Duration of exposure (n (%))		
≥1 day	52 (100.0)	51 (100.0)
≥1 week	50 (96.2)	51 (100.0)
≥2 weeks	49 (94.2)	51 (100.0)
≥4 weeks	48 (92.3)	50 (98.0)
≥8 weeks	47 (90.4)	49 (96.1)
≥12 weeks	46 (88.5)	47 (92.2)
≥16 weeks	45 (86.5)	47 (92.2)
≥20 weeks	45 (86.5)	46 (90.2)
≥24 weeks	42 (80.8)	43 (84.3)
≥28 weeks	41 (78.8)	43 (84.3)
32-35 weeks	41 (78.8)	41 (80.4)

In the randomized population, a majority of subjects received less than the intended full amount of study drug exposure at any visit in the SFP group (35 subjects, 64.8%) and in the placebo group (31 subjects, 57.4%).

Subject Disposition

A total of 108 patients with HDD-CKD were randomized, 103 (52 in the SFP group, 51 in the placebo group) received study drug . The majority of the subjects who received study drug

completed the study in the SFP (78.8%) and placebo (78.4%) groups. The most frequent primary reasons for withdrawal in both groups included withdrew consent and adverse event.

Table 22. Subject Disposition

	SFP	Placebo
Randomized	54	54
Stratum I	42 (77.8)	42 (77.8)
Stratum II	12 (22.2)	12 (22.2)
Received study drug	52	51
Did not receive study drug	2	3
Primary reason:		
Adverse Event		1
Other	2	
Protocol Violation		2
Completed study	41 (78.8)	40 (78.4)
Discontinued prematurely	11 (21.2)	11 (21.6)
Reason for discontinuation:		
Adverse event	3 (5.8)	3 (5.9)
Death	2 (3.8)	3 (5.9)
Protocol violation	1 (1.9)	1 (2.0)
Lost to follow-up	0 (0.0)	0 (0.0)
Withdrew consent	4 (7.7)	4 (7.8)
Sponsor's request	0 (0.0)	0 (0.0)
Principal Investigator decision	2 (3.8)	0 (0.0)
Other	1 (1.9)	3 (5.9)

Stratum I: ≤13,000 equivalent units/week epoetin; Stratum II: >13,000 equivalent units/week epoetin.

Protocol Violations/Deviations

Protocol deviations identified for the randomized subjects are summarized in Table below.

Table 23. Protocol Violations/Deviations

	SFP N=54 n (%)	**Placebo N=54 n (%)**
Received wrong treatment	2 (3.7)	2 (3.7)
Randomized to wrong stratum	1 (1.9)	4 (7.4)
Change in type of ESA	1 (1.9)	0 (0.0)
Did not meet inclusion/exclusion criteria	16 (29.6)	16 (29.6)
Did not receive study drug due to missing visit	25 (46.3)	26 (48.1)
Received less than the intended full amount of study drug exposure at any visit	35 (64.8)	31 (57.4)
IV iron deviation	6 (11.1)	9 (16.7)
Lack of adherence to centralized anemia management center- recommended	22 (40.7)	23 (42.6)
Other	38 (70.4)	44 (81.5)

Analyzed populations

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MITT population: Randomized subjects who received at least one dose of study drug and also received ESA during the treatment period.

Safety population: Safety population: Subjects who received any amount of study drug. Subjects receiving an incorrect treatment are summarized as SFP.

In NIH-FP-01, 2 subjects randomized to the placebo group who incorrectly received SFP for a few treatments were summarized in the SFP group in the safety population but were analyzed in the placebo group in the MITT population. All of the 103 subjects who received study drug were included in the safety and the MITT populations.

The number of subjects in analyzed populations for the study is shown below.

Table 24. Analyzed Populations

	SFP	**Placebo**
Randomized	54	54
MITT population	52	51
Safety population	54	49

3.2.2.2 Analysis of Primary Endpoint(s)

Change in Prescribed ESA Dose:

The mean change in prescribed ESA dose from baseline to end-of-treatment in the MITT population is shown in Table below. At end-of-treatment, the subjects receiving SFP had a mean increase of 7.3% in prescribed ESA dose while the placebo group had a mean increase of 37.3% in prescribed ESA dose. After adjusting for baseline Hgb, the SFP group had treatment difference in prescribed ESA dose from placebo with an LS mean difference of -35% with a calculated p value of 0.045.

Table 25. Change from Baseline in Prescribed ESA Dose in MITT Population

Prescribed ESA Dose [equivalent units of epoetin (U/week)	**SFP N=52**	**Placebo N=51**
Baseline, Mean (SD)	9483.2 (5413.9)	9205.9 (5500.1)
End-of-Treatment, Mean (SD)	9871.2 (7523.2)	12628.8 (13967.4)
Change from Baseline, Mean (SD)	387.9 (5556.2)	3422.9 (11641.9)

Change in %	7.3 (67.7)	37.3 (106.1)
ANCOVA with Covariate of Baseline Hgb		
LS Mean (SE)	4.9 (12.1)	39.8 (12.2)
95% CI of LS Mean	(-19.1, 28.8)	(15.7, 64.0)
LS Mean Difference from Placebo(SE)	-35.0 (17.20)	
95% CI of LS Mean Difference from Placebo	-69.1, -0.8	
p-value	0.045	

Change in Actual ESA Dose:

The mean change in actual ESA dose from baseline to end-of-treatment in the MITT population is shown in Table below. At end-of-treatment, the subjects receiving SFP had a mean 12.5% increase in actual ESA dose while the placebo group had a mean 42.2% increase in prescribed ESA dose. After adjusting for baseline Hgb, the SFP group had treatment difference in prescribed ESA dose from placebo with an LS mean value of -32.1% with a calculated p value of 0.098.

Table 26. Change from Baseline in Actual ESA Dose in MITT Population

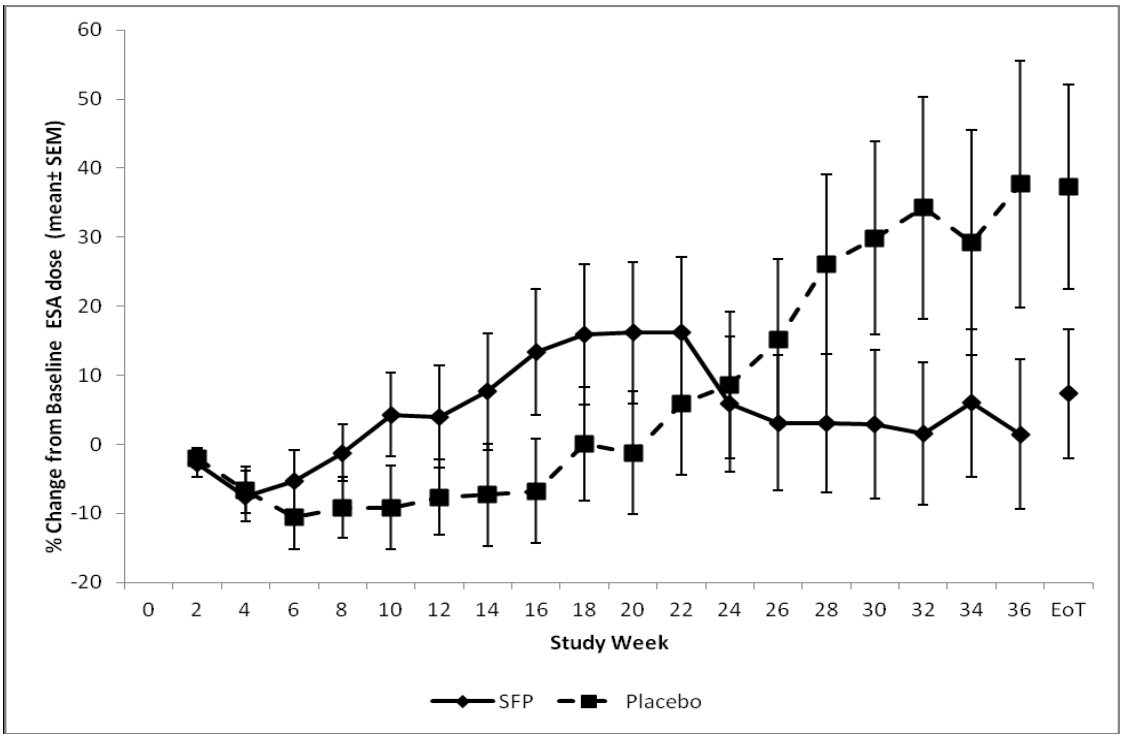
Prescribed ESA Dose [equivalent units of epoetin (U/week)	**SFP N=52**	**Placebo N=51**
Baseline, Mean (SD)	9177.5 (5505.07)	8835.6 (5449.02)
End-of-Treatment, Mean (SD)	9409.9 (7070.24)	12385.8 (13926.29)
Change from Baseline, Mean (SD)	232.4 (5581.01)	3550.2 (11467.55)
Change in %	12.5 (85.27)	42.2 (107.25)
ANCOVA with Covariate of Baseline Hgb		
LS Mean (SE)	11.3 (13.51)	43.4 (13.64)
95% CI of LS Mean	(-15.5, 38.1)	(16.4, 70.5)
LS Mean Difference from Placebo(SE)	-32.1 (19.26)	
95% CI of LS Mean Difference from Placebo	-70.3, 6.1	
p-value	0.098	

3.2.2.3 Analysis of Secondary Endpoints(s)

Changes from baseline in the prescribed ESA dose over time

The percent changes in prescribed ESA dose from baseline over time in the MITT population are displayed in the Figure below. After changes in ESA dosing were allowed at Week 5, the prescribed ESA dose was increased more in the SFP group during the period from Week 10 to Week 24 as compared to the placebo group. After Week 24, the prescribed ESA dose increased more in the placebo group as compared to the SFP group.

Figure 2. Changes from Baseline in Prescribed ESA Dose Over Time



ESA response index (ERI)

ERI was calculated as prescribed ESA dose (U/wk)/Hgb (g/L). The change in ERI from baseline to the end-of-treatment was smaller in the SFP group (99.9 U/wk/g/L) than in the placebo group (397.4 U/wk/g/L), but the difference was not statistically significant (p=0.304).

Table 27. Change in ESA Response Index

	SFP N=52	**Placebo N=51**
Baseline ERI		
N	52	51
Mean (SD)	868.0 (492.01)	834.6 (503.12)
End-of-Treatment ERI		
N	49	51
Mean (SD)	972.4 (756.04)	1231.9 (1337.54)
Change from baseline in ERI	99.9 (571.94)	397.4 (1132.67)
P-value	0.304	

Distribution of changes from baseline in the prescribed ESA dose

The distribution of magnitude of change in prescribed ESA dose from baseline to end-of-treatment did not show significant different (p=0.915) (see Table below).

Table 28. Distribution of changes from baseline in the prescribed ESA dose

Changes from baseline in the prescribed ESA dose	**SFP N=52 n (%)**	**Placebo N=51 n (%)**
Increase ≥ 25%	16 (30.8)	20 (39.2)
Increase 10 to <25%	5 (9.6)	4 (7.8)
Increase or decrease <10%	12 (23.1)	9 (17.6)
Decrease 10% to <25%	3 (5.8)	3 (5.9)
Decrease ≥ 25%	16 (30.8)	15 (29.4)
p-value	0.915	

Supplemental IV iron use

The use of supplemental IV iron at end-of-treatment is shown in the Table below. At end-of-treatment, fewer subjects received supplemental IV iron in the SFP group (11 subjects 21.2%) than in the placebo group (20 subjects, 39.2%). For subjects who received IV iron, the mean dose of supplemental IV iron at the end-of-treatment was similar in the SFP group (111.3 mg/week) and the placebo group (116.4 mg/week).

Table 29. Supplemental IV Iron Use

IV iron use at end of treatment	**SFP N=52**	**Placebo N=51**
Number of subjects who received IV iron (n, %)	11 (21.2)	20 (39.2)
Mean (SD) dose per subject who received IV iron (mg/week)	111.3 (65.2)	116.4 (41.3)
Median (mg/week)	100.0	102.5
Min, Max (mg/week)	63.0, 300.0	62.0, 233.3

3.3. Efficacy Summary

The efficacy of Triferic was evaluated in two randomized controlled phase 3 clinical trials (SFP-4 and SFP-5) in adult patients with hemodialysis-dependent chronic kidney disease (HDD-CKD) (305 patients in SFP-4 and 294 patients in SFP-5) for the proposed indication for the treatment of iron loss or iron deficiency to maintain hemoglobin. Both studies were multicenter, randomized, single-blind, placebo-controlled investigation of SFPstudy in iron-replete patients with HDD-CKD. Study patients received SFP in dialysate at the concentration of 110 μg iron/L or standard dialysate without SFP as placebo during each hemodialysis for 3 or 4 times per week during the randomized, controlled treatment period of the study. The mean treatment duration in the randomized phase was 157.7 days in the SFP group and 164.6 days in the placebo group in Study SFP-4 and 161.2 days in the SFP group and 157.9 days in the placebo group in Study

SFP-5. About 50% of study patients received study treatment for ≥20 weeks and 20% of study patients received study treatment for 44-47 weeks in the randomized phase.

The primary efficacy endpoint was the change in mean hemoglobin from baseline to the end of treatment period (last one-sixth of the randomized treatment period). In Study SFP-4, the mean hemoglobin decreased 0.03 g/dL in the SFP group as compared to a decrease of 0.38 g/dL in the placebo group in the ITT population. In Study SFP-5, the mean hemoglobin decreased 0.08 g/dL in the SFP group as compared to a decrease of 0.44 g/dL in the placebo group in the ITT population. The primary efficacy analysis used an ANCOVA analysis with baseline Hgb as the covariate. The treatment differences in hemoglobin calculated as LS mean difference was 0.35 g/dL in both studies between the SFP and the placebo groups and was statistically significant (p=0.01) in both studies. The results of additional analyses in MITT population and secondary endpoints in changes in TSAT and serum ferritin level from baseline to the end of treatment were consistent with the results from the primary efficacy analysis in both studies. The results from the two phase 3 clinical studies demonstrated that Triferic was effective to maintain hemoglobin during the treatment period in iron-replete patients with HDD-CKD in the studies as conducted.

A significant number of study patients were withdrawn from the both studies prior to the anticipated treatment duration of 48 weeks (45.4% in the SFP group and 53.6% in the placebo group in Study SFP-4; 46.3% in the SFP-group and 61.2% in the placebo group in Study SFP-5) due mainly to protocol-mandated anemia management. Of those withdrawn, the majority of study patients were due to required ESA dose change for hemoglobin in Study SFP-4 (42.8% in the SFP group and 45.1% in the placebo group) and in Study SFP-5 (44.2% in the SFP group and 46.9% in the placebo group) and a few patients were withdrawn due to requirement of intravenous iron administration for serum ferritin level <100 μg/L in Study SFP-4 (2.6% in the SFP group and 9.2% in the placebo group) and in Study SFP-5 (2.0% in the SFP group and 14.3% in the placebo group). Further analysis of the final hemoglobin and serum ferritin values prior to withdrawal showed that more patients in the SFP group (27%) as compared to the placebo group (20.9%) had hemoglobin >12 g/dL and more subjects in the placebo group as compared to the SFP group (17.6% vs. 11.2%, respectively) had hemoglobin <9 g/dL in Study SFP-4. There were also more subjects withdrawn who had serum ferritin level <100 μg/L in the placebo group as compared to the SFP group (11.1% vs. 3.3%, respectively). Similarly, in Study SFP-5, there were more subjects who had hemoglobin < 9 g/dL withdrawn in the placebo group as compared to the SFP group (23.1% vs. 15%, respectively) and more subjects withdrawn with hemoglobin >12 g/dL in the SFP group as compared to the placebo group (21.8% vs. 14.3%, respectively). There were also more subjects who had serum ferritin level <100 μg/L in the placebo group as compared to the SFP group (15.6% vs. 2.7%, respectively). These results were consistent with the primary efficacy results.

The efficacy of Triferic was evaluated in one phase 2 study (NIH-FP-01) in 103 patients for the proposed indication statement to reduce the prescribed dose of erythropoiesis stimulating agent (ESA) required to maintain desired hemoglobin levels. This was a multicenter, randomized, double-blind, placebo-controlled exploratory study in iron-replete patients with HDD-CKD. The mean treatment duration was 212 days in the SFP group and 222 days in the placebo group. The primary efficacy endpoint was the percent change from baseline in ESA dose at the end of

treatment. The results showed that the subjects receiving SFP had a mean increase of 7.3% in prescribed ESA dose at end-of-treatment as compared to a mean increase of 37.3% in the placebo group (p=0.045). However, the subjects receiving SFP had a mean 12.5% increase in actual ESA dose as compared to a mean 42.2% increase in the placebo group and the differences between the two treatment groups did not reach statistical significance (p=0.098). The secondary efficacy endpoint analysis showed a similar distribution of changes in the prescribed ESA dose between the SFP and the placebo groups (p=0.915). In addition, the NIH-FP-01 study protocol stated that this study was exploratory in nature and statistical tests were considered to be descriptive rather than conclusive. No formal sample size determination was provided in the protocol. Because of the inconsistent efficacy results and exploratory nature of the study, the submitted data is insufficient to support the proposed second indication to reduce the prescribed dose of ESA required to maintain desired hemoglobin levels.

FDA Statistical observations and comments for the statistical analysis plan and efficacy results for the SFP-4, SFP-5 and NHI-FP-01 studies are attached as Appendix 1 at the end of this document.

4 Clinical -- Safety

4.1 Safety Assessment

Studies/Clinical Trials Used to Evaluate Safety:

The following table lists the clinical studies used to evaluate overall safety of Triferic. Two Phase 3, randomized, placebo-controlled clinical trials (SFP-4 and SFP-5) in patients with HDD-CKD were used to evaluate the safety of Triferic for the proposed indication. Additional safety data from other clinical trials and open-label extension studies in patient with HDD-CKD were provided to support the safety of Triferic.

Table 30. Clinical Trials Used to Evaluate Safety

	SFP	**Placebo**	Total
Phase 3 Placebo-Controlled Studies			
SFP-4	149	151	300
SFP-5	143	145	288
Total	292	296	588
Other Controlled Studies			
SFP-1	10	11	21
SFP-2	105	26	131
SFP-3	32	0	32
SFP-6 (Crossover study)	693	686	703
NIH-FP-01 (02 DEC 2010 protocol version)	54	49	103

NIH-FP-01 (prior to 02 DEC 2010 protocol version)	5	6	11
Total	899	778	1001
Uncontrolled Open-Label Extension Studies			
SFP-4-OL	98	107 (received SFP)	205
SFP-5-OL	101	113 (received SFP)	214
SFP-6-OL	308	0	308
Total	507	220 (received SFP)	727
Total Number of Unique SFP Subjects in Clinical Trials	1411		

Adverse events (AEs) as reported on the case report forms (CRFs) were coded using MedDRA system organ class and preferred term.

The Integrated Analysis of Safety included pooled safety data from the two randomized, placebo-controlled Phase 3 studies (SFP-4 and SFP-5) in patients with HDD-CKD. All SFP-treated patients in all clinical trials were also pooled to provide additional safety evaluation.

Extent of Exposure:
Of the 588 patients with HDD-CKD who received at least 1 dose of study drug in the two Phase 3 clinical trials, 292 subjects received SFP and 296 subjects received placebo. The mean (SD) duration of exposure was 159.2 (112.9) days for the SFP group and 162.1 (110.9) days for the placebo group (see Table below). Slightly less than half of study patients received study treatment ≥20 weeks (46.6% in SFP and 50.7% in Placebo). In the SFP and placebo groups, respectively, 21.2% and 18.9% of subjects had ≥44 weeks of exposure. The total exposure to SFP in the pooled Phase 3 studies was 127.3 subject-years.

Table 31. Overall Drug Exposure in Pooled Phase 3 Clinical Studies

	SFP (N=292)	**Placebo (N=296)**
Duration of exposure (days)		
Mean (SD)	159.2 (112.9)	162.1 (110.9)
Median	128.0	143.0
Min, Max	1, 332	1, 333
Total exposure		
Subject-days	46493	47993
Subject-weeks	6641.9	6856.1
Subject-years	127.3	131.4
Distribution of duration of exposure, n (%)		
≥1 day	292 (100.0)	296 (100.0)
≥1 week	288 (98.6)	293 (99.0)
≥2 weeks	282 (96.6)	289 (97.6)
≥4 weeks	264 (90.4)	263 (88.9)
≥8 weeks	227 (77.7)	234 (79.1)

≥12 weeks	182 (62.3)	199 (67.2)
≥16 weeks	161 (55.1)	166 (56.1)
≥20 weeks	136 (46.6)	150 (50.7)
≥24 weeks	123 (42.1)	130 (43.9)
≥28 weeks	106 (36.3)	111 (37.5)
≥32 weeks	88 (30.1)	94 (31.8)
≥36 weeks	78 (26.7)	76 (25.7)
≥40 weeks	70 (24.0)	66 (22.3)
44-47 weeks	62 (21.2)	56 (18.9)

Reviewer's table

In pooled all clinical trials in the SFP clinical development program, a total of 1411 patients with HDD-CKD received at least one dose of SFP. This included three open-label extension safety studies (SFP-4-OL, SFP-5-OL, and SFP-6-OL) in the 120-day safety update submission. The mean (SD) duration of exposure of SFP in 1411 patients was 201.9 (175.9) days. A total of 863 subjects had ≥12 weeks of exposure to SFP, 734 subjects had ≥24 weeks of exposure to SFP, and 238 subjects had ≥52 weeks (1 year) of exposure to SFP (see Table below).

Table 32. Overall Drug Exposure in All Clinical Trials

	N=1411
Duration of exposure, days	
Mean (SD)	201.9 (175.85)
Median	180.0
Min, Max	1, 538
Total exposure	
Subject-days	284885
Subject-weeks	40697.9
Subject-years	780.0
Distribution of duration of exposure, n (%)	
≥1 day	1411 (100.0)
≥1 week	1381 (97.9)
≥2 weeks	1008 (71.4)
≥4 weeks	980 (69.5)
≥8 weeks	898 (63.6)
≥12 weeks	863 (61.2)
≥16 weeks	835 (59.2)
≥20 weeks	798 (56.6)
≥24 weeks	734 (52.0)
≥28 weeks	655 (46.4)
≥32 weeks	636 (45.1)

≥36 weeks	571 (40.5)
≥40 weeks	534 (37.8)
≥44 weeks	508 (36.0)
≥48 weeks	472 (33.5)
≥52 weeks	238 (16.9)
≥56 weeks	227 (16.1)
≥60 weeks	211 (15.0)
≥64 weeks	187 (13.3)
≥68 weeks	164 (11.6)
≥72 weeks	33 (2.3)
≥76 weeks	1 (0.1)

Demographics:

In the pooled Phase 3 clinical studies, the demographics in the safety population were similar between the SFP and placebo groups (see Table below). The mean (SD) age of subjects in the SFP and placebo groups was 59.0 (12.6) years (range, 20 to 86 years) and 59.6 (13.7) years (range, 21 to 89 years), respectively. The majority of subjects were Caucasian (52.7% in the SFP group and 56.1% in the placebo group) and male (61.3% in the SFP group and 66.2% in the placebo group).

Table 33. Demographics in Pooled Phase 3 Studies

	SFP (N=292)	**Placebo (N=296)**
Age (years)		
Mean (SD)	57.2 (12.6)	59.6 (13.7)
Median	59.0	60.0
Min, Max	20, 86	21, 89
Age Category, n (%)		
<65 years	210 (71.9)	188 (63.5)
≥65 years	82 (28.1)	108 (36.5)
Gender, n (%)		
Male	179 (61.3)	196 (66.2)
Female	113 (38.7)	100 (33.8)
Race, n (%)		
Caucasian	154 (52.7)	166 (56.1)
African American	112 (38.4)	99 (33.4)
Asian	14 (4.8)	9 (3.0)
Other	12 (4.2)	22 (6.5)

Among the total 1411 SFP-treated patients with HDD-CKD in all clinical trials in the SFP development program, the mean (SD) age was 58.8 (13.3) years with a range of 19 to 96 years. There were 967 (68.5%) patients <65 years of age and 444 (31.5%) patients ≥65 years of age. The majority of patients were male (61.7%) and most were Caucasian (50.8%).

Major Safety Results

The following table summarizes the overall adverse events in pooled Phase 3 clinical trials (SFP-4 and SFP-5).

Table 34. Overall Treatment-Emergent Adverse Events in Pooled Phase 3 Trials

Subject with Treatment-Emergent Adverse Events (AEs)	SFP (n=292) n (%)	Placebo (n=296) n (%)
TEAEs	229 (78.4)	223 (75.3)
Deaths	12 (4.1)	5 (1.7)
Nonfatal TESAEs	70 (24.0)	75 (25.3)
TEAEs leading to study discontinuation	13 (4.5)	7 (2.4)

Deaths

In the two Phase 3 clinical trials, 12 deaths (4.1%) occurred among the SFP-treated patients and 5 deaths (1.7%) occurred among the placebo-treated patients. The exposure-adjusted mortality rates were 9 deaths per 100 subject-years of exposure for SFP-treated patients and 4 deaths per 100 subject-years of exposure for placebo-treated patients.

The following table presents the all-cause deaths in each Phase 3 clinical trial.

Table 35. All-cause Deaths in Phase 3 Clinical Trials

	SFP-4		SFP-5	
	SFP (n=149) n (%)	Placebo (n=151) n (%)	SFP (N=143) n (%)	Placebo (N=145) n (%)
All-cause deaths	5 (3.4)	3 (2.0)	7 (4.9)	2 (1.4)

The following table summarizes the patients' information and adverse events leading to deaths for the two treatment groups. Among the death cases, the patient age range was similar between the two treatment groups. All deaths occurred in male patients except for three females in the SFP group. The duration on study treatment ranged from 8 to 328 days in the SFP-treated patients and 27 to 227 days. Time to event leading to deaths since last study drug ranged from 1 to 15 days in the SFP-treated patients and 1 to 3 days in the placebo-treated patients. The adverse events leading to deaths were cardiac arrest in 8 cases (6 in the SFP-treated patients and 2 in the placebo-treated patients), sudden deaths or unknown cause in 5 cases (4 in the SFP-treated

patients and 1 in the placebo-treated patients), acute MI in 3 cases (1 in the SFP-treated patients and 2 in the placebo-treated patients), and one case of bronchopneumonia in the SFP group.

Study name Treatment group	Age/ Gender Patient ID	Treatment duration (days on study)	Time to event leading to death since the last study drug	Time to death since the last study drug	AEs leading to death	Underlying conditions	Causality assessment by investigator

Table 36. Analysis of Death Cases in Pooled Two Phase 3 Trials

	SFP (N=292)	Placebo (N=296)
Total deaths	12 (4.1%)	5 (1.7%)
Age	44-72 years	47-79 years
Gender	9 Males, 3 Females	5 Males
Treatment duration on study drug	8-328 days	27-227 days
Time to event leading to death since last study drug	1-15 days	1-3 days
Event leading to death/cause of deaths		
Cardiac arrest	6	2
Sudden deaths/unknown	4	1
MI	1	2
Bronchopneumonia	1	0

Patient information for the death cases in each study is listed in the following table. Almost all patients had significant underlying cardiac conditions. Six of 12 patients in the SFP group and one of 5 patients in the placebo group died at home or nursing home without sufficient diagnosis made to allow meaningful assessment. None of death cases was considered to be related to the study treatment by investigator.

Table 37. Listing of Death Cases in Two Phase 3 Clinical Trials

Study SFP-4							
SFP group	68/M 406-032	8 days	5 days	5 days	Found unresponsive at nursing home, cardiac arrest	CAD, CHF, DM	Not related
	65/M 410-007	48 days	1 day	1 day	Unresponsive, died prior to paramedics arrived	CAD, HTN, DM	Not related
	68/M 432-008	45 days	3 days	3 days	SOB, light-headedness, cardiac arrest in ER	CAD, HTN, DM	Not related
	57/F 433-017	69 days	1 day	8 days	Chest pain, SOB, acute MI	CAD, HTN, COPD	Not related
	44/M 437-038	239 days	2 days	2 days	Found dead at home	DM, HTN	Not related
Placebo group	74/M 406-042	31 days	3 days	14 days	Trauma, cardiac arrest	CAD, CHF, DM	Not related
	47/M 436-009	227 days	3 days	6 days	Chest pain, acute MI	CAD, CHF	Not related
	71/M 437-043	220 days	3 days	25 days	SOB, cardiac arrest, CHF	CAD, MI, CVA, DM	Not related
Study SFP-5							
SFP group	66/M 514-002	22 days	1 day	1 day	Collapsed and unresponsive VT, cardiac arrest	CAD, HTN, MI	Not related
	72/M 526-007	188 days	15 days	15 days	Died at home due to cardio-respiratory arrest	DM, HTN, cardiac pacemaker	Not related
	49/M 526-027	328 days	2 days	3 days	Chest pain, cardiac arrest, pulmonary edema	DM, HTN	Not related
	56/F 530-014	148 days	2 days	2 days	Found expired at home	DM, CHF, HTN	Not related
	67/M 531-030	176 days	2 days	4 days	Bronchopneumonia	DM, CHF, testicular cancer	Not related
	66/F 531-040	108 days	2 days	2 days	Died at home "Sudden death"	CAD, DM, HTN	Not related
	59/M 555-021	120 days	14 days	Not provided	Cardiac arrest	DM, CHF, CAD, Stroke	Not related
Placebo group	79/M 512-016	73 days	2 days	2 days	Found dead at home Sudden death	CAD, HTN, Aortic aneurysm	Not related
	75/M 519-019	27 days	1 day	2 days	Chest pain, acute MI	CAD, DM, HTN	Not related

In all clinical trials including the open-label extension studies in 1411 SFP-treated patients with HDD-CKD, 51 (3.6%) deaths were reported. The exposure-adjusted mortality rate for all SFP-treated subjects was 6.5 deaths per 100 subject exposure years). Most deaths were considered to be cardiac related. No deaths were considered by the investigator to be related to SFP treatment. The following table summarizes the patient's demographics and AEs leading to deaths.

Table 38. Summary of Deaths in SFP-treated Patients in All Clinical Trials

	All SFP-treated Patients (n=1411)
Total deaths	51 (3.6%)
Age	25-93 years
Gender	33 Males, 18 Females
Treatment duration on study drug	12-491 days
Reported Events Leading to Death	
Cardiac arrest	17
Cardio-respiratory arrest	7
Death	4
Myocardial infarction	4
Arteriosclerosis coronary artery	3
Sudden death	3

Hypoxic-ischemic encephalopathy	2
Septic shock	2
Acute respiratory failure	1
Azotemia	1
Bronchopneumonia	1
Electrolyte imbalance	1
Gastroenteritis	1
Gastrointestinal hemorrhage	1
Hepatic failure	1
Intestinal perforation	1
Pneumonia	1
Sepsis	1
Shock	1
Subdural hematoma	1
Ventricular arrhythmia	1

One of the deaths occurred at the same day Triferic was administered during hemodialysis. The patient narrative is shown below.

Subject Number 1182-027
This a 68-year-old black or African American man with HDD-CKD who was enrolled in the RMTI-SFP-6 double-blind crossover study on (b) (6) (Study Day -21). He was randomly assigned on 08 Oct 2012 to receive SFP from Weeks 1-2 and placebo from Weeks 4-5. The subject received his first dose of study drug in the double-blind crossover study on (b) (6) (Study Day 1). On 16 Nov 2012, the subject signed the informed consent for the RMTI-SFP-6 open-label long-term extension study and received his first dose of open-label SFP on (b) (6) (Study Day 64; Extension Study Day 1). Chronic kidney disease had been diagnosed on 11 Feb 2012 and the subject had received his first dialysis treatment on 11 Feb 2012. Additional significant medical history included myocardial infraction, congestive cardiac failure, type 2 diabetes mellitus, diabetic neuropathy, hyperlipidemia, hypertension, leg amputation, peripheral vascular disorder, secondary hyperparathyroidism, and unilateral blindness.

The subject's last dose of SFP had been administered on (b) (6) (Study Day 379; Extension Study Day 316). On (b) (6), the subject started dialysis at his usual time of 05:30 AM. Dialysis was completed at 09:34 AM, and at the end of the subject's 4-hour dialysis session, the vital signs were recorded as pulse rate 91 bpm, blood pressure 117/70 mm Hg, and respiratory rate 16 breaths per minute. Post-treatment, the subject passed out and cardiopulmonary resuscitation was performed until an ambulance arrived to transport him to the hospital. On the way to the hospital, the subject experienced a cardiac arrest. At 10:11 AM, the subject arrived at the emergency room in a ventricular fibrillation rhythm with cardiopulmonary resuscitation in progress. A cardiac arrest code was performed. Treatment for the event included amiodarone hydrochloride. At (b) (6) the code was called off and the subject was pronounced dead. An autopsy was not performed. According to the death certificate, the cause of death was cardiopulmonary arrest and atherosclerotic heart disease. The event was considered to be related to study drug by the investigator.

Nonfatal Serious Adverse Events

In SFP-4 and SFP-5 studies combined 24.0% of the SFP-treated patients and 25.3% of the placebo-treated patients experienced at least one nonfatal treatment-emergent serious adverse events (TESAEs). A total of 120 TESAEs were reported in the SFP group and 154 TESAEs were

reported in the placebo group. The following table includes nonfatal TESAEs reported in ≥1% of SFP-treated patients.

Table 39. Treatment-Emergent Serious Adverse Events Reported ≥1% of SFP-treated Subjects in Pooled SFP-4 and SFP-5 Studies

System organ class Preferred term	SFP N=292 n (%)	Placebo N=296 n (%)
Number of subjects with ≥1 TESAE	70 (24.0)	75 (25.3)
Cardiac disorders	12 (4.1)	22 (7.4)
Cardiac failure congestive	5 (1.7)	7 (2.4)
General disorders and administration site conditions	6 (2.1)	7 (2.4)
Non-cardiac chest pain	3 (1.0)	7 (2.4)
Infections and infestations	21 (7.2)	22 (7.4)
Pneumonia	5 (1.7)	8 (2.7)
Diabetic foot infection	3 (1.0)	0 (0.0)
Injury, Poisoning and Procedural Complications	14 (4.8)	10 (3.4)
Arteriovenous fistula thrombosis	5 (1.7)	2 (0.7)
Metabolism and Nutrition Disorders	8 (2.7)	20 (6.8)
Fluid overload	4 (1.4)	13 (4.4)
Respiratory, Thoracic and Mediastinal Disorders	5 (1.7)	6 (2.0)
Pulmonary edema	4 (1.4)	1 (0.3)

The nonfatal TESAEs that were reported more frequently in the SFP group as compared to the placebo group were diabetic foot infection (1% vs. 0%), arteriovenous fistula thrombosis (1.7% vs. 0.7%), and pulmonary edema (1.4% vs. 0.3%). There were no nonfatal TESAEs in the SFP or placebo groups that were considered by the investigator to be related to study treatment.

Of the 1411 SFP-treated subjects in SFP clinical development program, 412 subjects (29.2%) experienced a total of 899 nonfatal TESAEs. The most common TESAEs, occurring in ≥1% of subjects were fluid overload (2.3%), hyperkalemia (2.0%), pneumonia (1.8%), congestive heart failure (1.7%), arteriovenous fistula thrombosis (1.3%), pulmonary edema (1.3%), acute myocardial infarction (1.1%), atrial fibrillation (1.1%), non-cardiac chest pain (1.1%), coronary artery disease (1.0%), and vascular graft thrombosis (1.0%).

A total of 5 subjects (0.4%) experienced TESAEs considered by the investigator to be related to study treatment. These TESAEs were pneumonia in 2 patients, abdominal pain, pyrexia, and leukocytoclastic vasculitis each in one patient.

Dropouts and/or Discontinuations

Overall, 13 (4.5%) patients had at least one TEAE that leading to treatment discontinuation in the SFP group as compared to 7 (2.4%) patients in the placebo group in the Phase 3 studies. The most common TEAEs leading to study discontinuation in the SFP group were asthenia, dizziness, and headache, occurring in 2 subjects each (0.7%). All other TEAEs that led to study discontinuation occurred in single subjects including thrombocytopenia, cardiac arrest, coronary artery disease, blurry vision, constipation, feeling cold, feeling hot, flushing, nausea, hypotension, hypersensitivity, vascular graft complication (arm pain during administration), hemoglobin decreased, worsening peripheral neuropathy, flushing, and pruritus generalized.

Table 40. Treatment-Emergent Adverse Events Leading to Study Discontinuation in ≥1 SFP-treated Subject

System organ class **Preferred term**	**SFP** **N=292**	**Placebo** **N=296**
Number of subjects with ≥1 TEAE leading to study discontinuation	13 (4.5)	7 (2.4)
Blood and Lymphatic System Disorders	1 (0.3)	0 (0.0)
Thrombocytopenia	1 (0.3)	0 (0.0)
Cardiac Disorders	2 (0.7)	0 (0.0)
Cardiac arrest	1 (0.3)	0 (0.0)
Coronary artery disease	1 (0.3)	0 (0.0)
Eye Disorders	1 (0.3)	0 (0.0)
Vision blurred	1 (0.3)	0 (0.0)
Gastrointestinal Disorders	1 (0.3)	2 (0.7)
Constipation	1 (0.3)	0 (0.0)
General Disorders and Administration Site Conditions	2 (0.7)	2 (0.7)
Asthenia	2 (0.7)	1 (0.3)
Feeling cold	1 (0.3)	0 (0.0)
Feeling hot	1 (0.3)	0 (0.0)
Injury, Poisoning and Procedural Complications	2 (0.7)	0 (0.0)
Procedural hypotension	1 (0.3)	0 (0.0)
Vascular graft complication	1 (0.3)	0 (0.0)
Investigations	1 (0.3)	1 (0.3)
Hemoglobin decreased	1 (0.3)	1 (0.3)
Nervous System Disorders	4 (1.4)	2 (0.7)
Dizziness	2 (0.7)	1 (0.3)
Headache	2 (0.7)	0 (0.0)
Neuropathy peripheral	1 (0.3)	0 (0.0)
Skin and Subcutaneous Tissue Disorders	1 (0.3)	0 (0.0)
Pruritus generalized	1 (0.3)	0 (0.0)

In 7 of 13 SFP-treated patients, treatment-related TEAEs that led to study discontinuation determined by investigator were asthenia, dizziness, and headache, blurry vision, thrombocytopenia (also on heparin), flushing, nausea, cramping, hypotension, constipation, feeling cold, feeling hot, and procedural hypotension.

The patient who experienced procedural hypotension was also considered to be a suspected hypersensitivity reaction by the investigator.

In all clinical trials in a total of 1411 SFP-treated subjects in the SFP development program, 49 subjects (3.5%) experienced a total of 62 TEAEs that led to study treatment discontinuation. The most common TEAEs leading to study discontinuation were acute myocardial infarction and headache (3 subjects each, 0.2%), cardiac arrest, coronary artery disease, dizziness, asthenia, constipation, and generalized pruritus (2 subjects, 0.1%).

Fourteen (1.0%) of the 1411 SFP-treated subjects had treatment-related TEAEs that led to study discontinuation. The treatment-related TEAEs that led to study discontinuation were headache (3 subjects, 0.2%); constipation, asthenia, and dizziness (2 subjects each, 0.1%); and thrombocytopenia (on heparin), vision blurred, nausea, feeling cold, feeling hot, pyrexia, hyperbilirubinemia, drug hypersensitivity, procedural hypotension, hepatic enzyme increased, and generalized pruritus (1 subject each, 0.1%).

The treatment-related TEAE of drug hypersensitivity that led to study discontinuation was also considered to be a suspected hypersensitivity reaction by the investigator.

The TEAEs of hyperbilirubinemia and hepatic enzyme increased that led to study discontinuation were experienced by the same subject and were assessed as possibly related to study drug by the investigator. A significant increase in alkaline phosphatase (1710 U/L) and total bilirubin (111.15 µmol/L) above baseline levels with lesser increases in transaminases (ALT 79 U/L and AST 72 U/L; <2 xULN) was reported. This subject had elevated enzymes prior to the first dose of SFP and was subsequently diagnosed with cholelithiasis.

Adverse events of special interest (AESIs)

The AESIs included the following adverse events:

- Intradialytic hypotension (IDH)
- Suspected Hypersensitivity Reactions
- Composite Cardiovascular Events
- HD Vascular Access Thrombotic Events
- Other Venous or Arterial Thrombotic Events
- Systemic/Serious Infections

The following table summarizes the AESIs in pooled two phase 3 clinical trials.

Table 41. Treatment-Emergent Adverse Events of Special Interest in Pooled Phase 3 Trials

TEAEs of Special Interest	SFP N=292	Placebo N=296
Intradialytic hypotension, n (%)	62 (21.2)	57 (19.3)
Symptomatic	26 (8.9)	19 (6.4)
Requiring Intervention	35 (12.0)	36 (12.2)
Suspected Hypersensitivity Reactions, n (%)	1 (0.3)	0 (0.0)
Composite Cardiovascular Events, n (%)	26 (8.9)	27 (9.1)
HD Vascular Access Thrombotic Events, n (%)	15 (5.1)	11 (3.7)
Arteriovenous fistula or graft thrombosis	13 (4.5)	10 (3.4)
HD catheter thrombosis	2 (0.7)	2 (0.7)
Other Thrombotic Events, n (%)	3 (1.0)	6 (2.0)
Systemic/Serious Infections, n (%)	24 (8.2)	26 (8.8)

Intradialytic hypotension (IDH)

In the pooled two Phase 3 trials, 292 SFP-treated patients received the total of 19950 HD sessions and 296 placebo-treated patients received a total of 20398 HD sessions. IDH episodes occurred at the same rate (2.1% of the total HD sessions) in both treatment groups. There were similar frequencies of IDH episodes resulting in premature termination or interruption of dialysis between the SFP and placebo groups. Of those, the IDH episodes of a severity or frequency that exceeded the subject's established pattern of IDH prior to entering the study were also reported at similar frequencies: 1.4% of HD sessions in the SFP group and 1.2% in the placebo group. The overall incidence of subjects experiencing ≥1 IDH episode was 28.8% in the SFP group and 30.4% in the placebo group. However, the CRF did not have separate questions for whether the SBP decrease met the protocol definition of IDH and whether it exceeded the subject's established pattern of IDH prior to entering the study.

Table 42. Intradialytic Hypotension Episodes in Hemodialysis Sessions

	SFP (N=292) n (%)	Placebo (N=296) n (%)
Actual total number of HD sessions	19950	20398
Actual total number of HD sessions per subject, mean (SD)	68.3 (48.4)	68.9 (47.1)
HD sessions with an IDH episode, number of sessions (%)	416 (2.1)	420 (2.1)
Hypotension resulting in premature termination or interruption of dialysis	170 (0.9)	199 (1.0)
Decrease in SBP meeting the protocol definition of IDH	267 (1.3)	244 (1.2)
HD sessions with an IDH episode of a severity or frequency that exceeded the subject's established pattern of IDH prior to entering the study, number of sessions (%)	273 (1.4)	246 (1.2)
Hypotension resulting in premature termination or interruption of dialysis	17 (0.1)	19 (0.1)

Decrease in SBP meeting the protocol definition of IDH*	267 (1.3)	244 (1.2)
Number of subjects experiencing ≥1 IDH episode, n (%)	84 (28.8)	90 (30.4)
Hypotension resulting in premature termination or interruption of dialysis	48 (16.4)	48 (16.2)
Decrease in SBP meeting the protocol definition of IDH	57 (19.5)	58 (19.6)

*The CRF did not ask separate questions for whether the SBP decrease met the protocol definition of IDH and whether it exceeded the subject's established pattern of IDH prior to entering the study.

Intradialytic hypotension episodes that met both protocol-specified criteria for IDH reportable as an AE were reported as procedural hypotension in 62 subjects (21.2%) in the SFP group and 57 subjects (19.3%) in the placebo group (see Table below). There were 316 IDH events total (269 asymptomatic events and 47 symptomatic events) reported in the SFP group and 284 (236 asymptomatic events and 48 symptomatic events) in the placebo group. A subject may have experienced asymptomatic IDH episodes and symptomatic IDH episodes in different HD sessions during the treatment period.

Of subjects who had IDH episodes reported as TEAEs, 26 subjects (8.9%) in the SFP group as compared to 19 subjects (6.4%) in the placebo group reported ≥1 symptom; 35 subjects (12.0%) in the SFP group and 36 subjects (12.2%) in the placebo group required intervention.

The most commonly reported symptoms in both groups were dizziness or fainting, followed by muscle cramps, and nausea. The most common type of intervention in both groups was IV saline or other isotonic solution and terminating or reducing ultrafiltration. See Table below.

Table 43. Treatment-Emergent Intradialytic Hypotension Adverse Events

	SFP (N=292)		**Placebo (N=296)**	
	Events N	**Subjects n (%)**	**Events n**	**Subjects n (%)**
Any TEAE that met both protocol criteria for IDH reportable as an AE	316	62 (21.2)	284	57 (19.3)
Asymptomatic IDH TEAE with ≥1	141	23 (7.9)	111	27 (9.1)
IDH TEAE with ≥1 symptom	47	26 (8.9)	48	19 (6.4)
Symptomatic IDH TEAE with at least 1 intervention	38	23 (7.9)	43	17 (5.7)
Asymptomatic	269	49 (16.8)	236	49 (16.6)
Not requiring intervention	127	38 (13.0)	125	33 (11.1)
Requiring intervention[a]	141	23 (7.9)	111	27 (9.1)
IV saline or other isotonic solution	69	19 (6.5)	47	23 (7.8)
Terminating or reducing ultrafiltration	100	12 (4.1)	75	12 (4.1)
Stopping dialysis altogether	3	2 (0.7)	2	2 (0.7)
Low temperature dialysate	1	1 (0.3)	0	0 (0.0)
Other	20	4 (1.4)	11	5 (1.7)
Symptomatic	47	26 (8.9)	48	19 (6.4)

Dizziness or fainting	24	16 (5.5)	14	10 (3.4)
Muscle cramps	9	6 (2.1)	11	6 (2.0)
Nausea	4	4 (1.4)	5	3 (1.0)
Abdominal discomfort	1	1 (0.3)	0	0 (0.0)
Vomiting	0	0 (0.0)	3	3 (1.0)
Other	19	13 (4.5)	25	10 (3.4)
Not requiring intervention	9	8 (2.7)	5	5 (1.7)
Requiring intervention[a]	38	23 (7.9)	43	17 (5.7)
IV saline or other isotonic solution	21	17 (5.8)	37	16 (5.4)
Terminating or reducing ultrafiltration	17	13 (4.5)	19	9 (3.0)
Stopping dialysis altogether	7	3 (1.0)	9	5 (1.7)
Other	7	3 (1.0)	8	4 (1.4)

Note: An IDH AE may have more than one symptom or intervention.

One subject (0.3%) in the SFP group reported a TEAE of IDH (PT: procedural hypotension) that led to study discontinuation; no TEAEs of IDH that led to study discontinuation were reported in the placebo group. The event was determined by the investigator to be a suspected hypersensitivity event (described in section below). Recorded symptoms included nausea, dizziness or fainting, and other symptoms. The subject was treated with IV saline and the event resolved on the same day.

In all clinical trials in 1411 SFP-treated subjects in SFP development program, 262 (18.6%) experienced any TEAE of IDH including 142 subjects (10.1%) who were asymptomatic requiring intervention and 141 subjects (10.0%) who reported ≥1 symptom. Similarly, the most common type of intervention was IV saline or other isotonic solution (112 of 142 asymptomatic subjects who required intervention and 108 of 131 symptomatic subjects who required intervention), and terminating or reducing ultrafiltration (78 of 142 asymptomatic subjects who required intervention and 71 of 131 symptomatic subjects who required intervention). The most commonly reported symptoms were dizziness or fainting (66 of 141 symptomatic subjects). Treatment-emergent SAEs of IDH occurred in 6 of 1411 SFP-treated subjects (0.4%).

Suspected hypersensitivity reactions

In Phase 3 trials, the suspected hypersensitivity reaction was reported in one (0.3%) patient (procedural hypotension) in the SFP group and none in the placebo group.

The following is patient narrative of this case.

Subject RMTI-SFP-5 544-001
This was a 61-year old man with HDD-CKD who received the first dose of SFP 2 μM (11 μg of iron/dL of dialysate) on 21 Sep 2011 (Day 1). Renal history for the subject included CKD since an unknown date secondary to diabetes mellitus type 2. Other significant medical conditions included renal cell carcinoma (in remission),

hypertension, aortic valve stenosis, right bundle branch block, allergic rhinitis and hepatitis, drug hypersensitivity (hydralazine), dyslipidemia, depression, and peripheral edema. Concomitant medications at the time of the event were simvastatin, glipizide, sevelamer carbonate, Vicodin®, alprazolam, cinacalcet hydrochloride, ergocalciferol, calcitriol, Renaplex ®, and sodium chloride.

The subject's last dialysis treatment prior to the event and his last dose of stage 2 study drug was on 21 Sep 2011 (Day 1).

On 21 Sep 2011 (Day 1), the subject experienced flushing two minutes after starting dialysis. Flushing lasted for a few seconds and then subsided. The subject's BP at the start of dialysis (2 minutes prior to the onset of flushing) was 160/85 mmHg and was 141/73 mmHg 23 minutes after the onset of flushing. Two hours and 40 minutes after the start of dialysis, the subject developed decreased BP of 85/54 mmHg and was diagnosed with procedural hypotension associated with cramping, nausea, and dizziness. On the same day 21 Sep 2011 (Day 1), the study drug was permanently discontinued in response to this event (procedural hypotension). The subject was treated with a normal saline IV bolus, which resulted in increase in BP to 104/56 mmHg within 10 minutes. The subject also received diphenhydramine and metoclopramide for flushing and nausea, respectively. The subject completed dialysis with SFP after a total of 4 hours and left the dialysis center in stable condition. The event of procedural hypotension was considered resolved without sequelae on 21 Sep 2011 (Day 1). The Investigator considered the treatment-emergent event of procedural hypotension as moderate and related to study drug. The event of procedural hypotension was considered to be suspected hypersensitivity reaction by the investigator.

In all clinical trials in 1411 SFP-treated patients in the SFP development program, suspected hypersensitivity reactions were reported for 6 (0.4%) subjects including one case in Phase 3 trials mentioned above. These events were reported as procedural hypotension [3 subjects], drug hypersensitivity [1 subject], syncope [1 subject], procedural pain [1 subject], and muscle spasms [1 subject]). These events were considered to be suspected hypersensitivity reactions by the investigators.

There were 3 additional patients (RMTI-SFP-4 402-013, RMTI-SFP-4 437-033, and RMTI-SFP-5 530-048) with AEs of procedural hypotension, procedural hypotension, and hypoesthesia [2 events], respectively) reported in ongoing open-label extension studies as suspected hypersensitivity reactions in the initial NDA submission. However, in the 120-safety update submission, the applicant indicated that the suspected hypersensitivity reaction questions on the AE CRFs in these patients had been marked in error and were corrected prior to database lock in the open-label extension studies.

Two of 6 suspected hypersensitivity reactions were considered to be treatment-related TEAEs (procedural hypotension and drug hypersensitivity) including one case in Phase 3 trials mentioned above. Both patients experienced TEAEs right after starting the first hemodialysis with SFP and those TEAEs led study treatment discontinued permanently.

The patient narrative for the additional case is presented below.

Subject RMTI-SFP-4 410-025
This was a 54-year-old woman with HDD-CKD who had previously received placebo during Stage 2. The subject entered the open-label long-term Stage 3 extension study on 30 APR 2012 and received her first and only dose of SFP on 02 MAY 2012 (Day 43; Extension Day 1). At the first visit at which the subject was exposed to SFP study drug, she experienced a non-serious event of drug hypersensitivity (allergic reaction to study drug). She had started dialysis at 05:02 and immediately developed symptoms of itching and a sensation of neck swelling; she also

developed a rash around the cheeks and neck. There were no symptoms of wheezing or chest tightness. She was being dialyzed using an Asahi Rexeed Polysulfone (HF) 25R dialyzer that had been previously used 3 times and cleaned with Renalin. She was given diphenhydramine 50 mg IV, and the bicarbonate jug was switched from one containing SFP to one without SFP. The event resolved without sequelae within 18 minutes at 05:20 on the same day (Day 43; Extension Day 1). Her blood pressure was 152/76 mmHg prior to dialysis at 04:57, and was 155/74 mmHg at 05:24. Dialysis was continued without further incident, ending at 08:10, and the subject left the clinic at 08:30. The subject was called later that day at 11:00 and it was confirmed that she remained clinically stable. The study drug was permanently discontinued on the same day (Day 43; Extension Day 1) in response to this event. The investigator considered the treatment-emergent event of drug hypersensitivity to be of moderate severity and probably related to study drug. The Sponsor medical monitor considered this treatment-emergent event to be non-serious and relatively mild, as it was not associated with decreased blood pressure and resolved with 50 mg diphenhydramine, and possibly related to study drug.

The following table summarizes the all six cases of suspected hypersensitivity reactions reported in all clinical trials.

Table 44. Cases of Suspected Hypersensitivity Reactions in All Clinical Trials

Study Subject ID Age/Gender	Time to onset of AEs	SFP dose/duration	Adverse Events	Required Treatment/Outcome	Causality assessment by investigator
SFP-4 OL 410-025 54 yrs/F	immediately	Extension Day 1 1st dose (received Placebo at Stage 2)	Itching, sensation of neck swelling, rash around cheeks and neck	Diphenhydramine 50 mg IV Switched to standard dialysate Resolved within 18 minutes Discontinued treatment permanently	Probably Related
SFP-5 544-001 62 yrs/M	2 min	1st dose	Flushing, Hypotension (2 hr 40 min) Cramping, nausea, and dizziness	Normal saline 400 ml IV bolus Ultrafiltration turned off BP increased in 10 minutes Diphenhydramine 25 mg orally Metoclopramide 5 mg orally Completed dialysis after a total of 4 hrs Resolved Discontinued treatment permanently	Related
NIH-FP-01 16-40 61 yrs/M	4 hrs	Day 160 on study	Worsening of intradialytic hypotension after completing dialysis	No treatment Resolved Continued SFP for 3 more months until completing the study	Not related
SFP-4 OL 421-021 46 yrs/M	Pre-dialysis	Extension Day 353 (Received SFP group at Stage 2)	Hypertension treated with clonidine and taken off dialysis Unresponsive/syncope with decreased BP in 1 hr 16 min	Hospitalized for syncope Resolved Completed Stage 3 to Day 491	Not related

SFP-6 1301-023 66 yrs/F	9 min	2nd dose	Intradialytic back pain Decreased SBP	Acetaminophen Decreased dialysis blood flow rate to 250 mL/min Resolved in 2 hours 20 minutes Completed dialysis	Not related
SFP-6 1461-015 60 yrs/M	3 hours	2nd dose	Intradialytic hypotension and worsening muscle cramping	IV normal saline 200 ml Dialysis interrupted temporally Completed dialysis Resolved Enrolled extension study and received 40 week treatment	Not related

Reviewer's table

Composite Cardiovascular Events

In the pooled Phase 3 studies, the rate of treatment-emergent composite cardiovascular events was similar between the two treatment groups. Overall, 26 subjects (8.9%) experienced 30 composite cardiovascular events in the SFP group as compared to 27 subjects (9.1%) experienced 42 composite cardiovascular events in the placebo group. Most events were considered to be serious. The most common cardiovascular TEAEs were congestive cardiac failure, cardiac arrest, and acute myocardial infarction. The cardiac arrest events were reported as fatal events that were discussed in the earlier section.

Table 45. TEAEs of Composite Cardiovascular Events in Pooled Phase 3 Studies

	SFP (N=292) n (%)	**Placebo (N=296) n (%)**
Number of Subjects with At Least One Treatment-Emergent Adverse Event of Composite Cardiovascular Event	26 (8.9)	27 (9.1)
Cardiac Disorders	23 (7.9)	25 (8.4)
Cardiac Failure Congestive	5 (1.7)	8 (2.7)
Cardiac Arrest	5 (1.7)	1 (0.3)
Acute Myocardial Infarction	4 (1.4)	6 (2.0)
Coronary Artery Disease	2 (0.7)	3 (1.0)
Angina Pectoris	2 (0.7)	2 (0.7)
Angina Unstable	2 (0.7)	0 (0.0)
Atrial Fibrillation	1 (0.3)	3 (1.0)
Cardio-Respiratory Arrest	1 (0.3)	2 (0.7)
Myocardial Infarction	1 (0.3)	2 (0.7)
Supraventricular Tachycardia	1 (0.3)	2 (0.7)
Cardiomegaly	1 (0.3)	0 (0.0)
Atrial Flutter	0 (0.0)	2 (0.7)
Atrioventricular Block First Degree	0 (0.0)	1 (0.3)
Cardiogenic Shock	0 (0.0)	1 (0.3)
Cardiomyopathy	0 (0.0)	1 (0.3)
Palpitations	0 (0.0)	1 (0.3)
General Disorders And Administration Site Conditions	2 (0.7)	1 (0.3)
Sudden Death	2 (0.7)	1 (0.3)

Nervous System Disorders	1 (0.3)	1 (0.3)
Cerebrovascular Accident	1 (0.3)	1 (0.3)

In all clinical trials in the overall 1411 SFP-treated subjects with HDD-CKD in the SFP development program, 139 subjects (9.9%) reported at least 1 composite cardiovascular event and 126 subjects (8.9%) had ≥1 serious composite cardiovascular TEAE. The most common composite cardiovascular TEAEs were congestive cardiac failure (2.1%), acute myocardial infarction (1.4%), cardiac arrest (1.3%), atrial fibrillation (1.1%), and coronary artery disease (1.0%).

HD Vascular Access Thrombotic Events and Other Thrombotic Events

In the pooled Phase 3 trials, overall HD vascular thrombotic events/other thrombotic events were reported at a similar rate between the two groups (see Table below). In the SFP group, 18 (6.2%) subjects experienced 22 HD vascular access/other thrombotic events; six (2.1%) had events that were considered to be serious. In the placebo group, 17 (5.7%) subjects experienced 23 HD vascular access/other thrombotic events; six (6, 2.0%) had events that were considered to be serious. The only event occurring more frequently in the SFP group as compared to the placebo was arteriovenous fistula thrombosis (3.4% and 2.0%, respectively).

Table 46. Hemodialysis Vascular Access Thrombotic Events and Other Thrombotic Events in Pooled Phase 3 Studies

	SFP (N=292) n (%)	**Placebo (N=296) n (%)**
Number of Subjects with At Least One Treatment-Emergent Adverse Event of HD Vascular Access/Other Thrombotic Event	18 (6.2)	17 (5.7)
General Disorders and Administration Site Conditions	5 (1.7)	5 (1.7)
Thrombosis In Device	5 (1.7)	5 (1.7)
Injury, Poisoning and Procedural Complications	13 (4.5)	10 (3.4)
Arteriovenous Fistula Thrombosis	10 (3.4)	6 (2.0)
Vascular Graft Thrombosis	3 (1.0)	4 (1.4)
Vascular Disorders	0 (0.0)	3 (1.0)
Deep Vein Thrombosis	0 (0.0)	3 (1.0)

In all clinical trials in 1411 SFP-treated subjects, 157 subjects (11.1%) had ≥1 TEAE of HD vascular access thrombotic events or other thrombotic events. The most common events were arteriovenous fistula thrombosis (63, 4.5%), vascular graft thrombosis (53, 3.8%), and thrombosis in device (45, 3.2%). Treatment-emergent SAEs of HD vascular access thrombotic events/other thrombotic events occurred in 37 subjects (2.6%).

Systemic/Serious Infections

In the pooled Phase 3 trials, the overall rate of systemic/serious infection reported was similar between the SFP and the placebo group (see Table below). In the SFP group, 24 (8.2%) subjects experienced 28 systemic/serious infection events; 23 (7.9%) had events that were considered serious events. In the placebo group, 26 (8.8%) subjects experienced 28 systemic/serious infection events; 25 (8.4%) had events that were considered serious events. The most common events were pneumonia (2.1%), urinary tract infection (1%), and diabetic foot infection (1%) in the SFP-treated patients.

Table 47. Systemic/Serious Infections in Pooled Phase 3 Studies

	SFP (N=292) n (%)	**Placebo (N=296) n (%)**
Number of Subjects with At Least One Treatment-Emergent Adverse Event of Systemic/Serious Infection	24 (8.2)	26 (8.8)
Pneumonia	6 (2.1)	8 (2.7)
Urinary Tract Infection	3 (1.0)	1 (0.3)
Diabetic Foot Infection	3 (1.0)	0 (0.0)
Cellulitis	2 (0.7)	1 (0.3)
Lobar Pneumonia	2 (0.7)	1 (0.3)
Device Related Sepsis	2 (0.7)	0 (0.0)
Sepsis	2 (0.7)	0 (0.0)
Gastroenteritis Viral	1 (0.3)	1 (0.3)
Osteomyelitis	1 (0.3)	1 (0.3)
Postoperative Wound Infection	1 (0.3)	0 (0.0)
Septic Shock	1 (0.3)	0 (0.0)
Urosepsis	1 (0.3)	0 (0.0)
Viral Upper Respiratory Tract Infection	1 (0.3)	0 (0.0)
Arteriovenous Graft Site Infection	0 (0.0)	2 (0.7)
Bacteremia	0 (0.0)	2 (0.7)
Upper Respiratory Tract Infection	0 (0.0)	2 (0.7)
Arteriovenous Fistula Site Infection	0 (0.0)	1 (0.3)
Bronchitis	0 (0.0)	1 (0.3)
Device Related Infection	0 (0.0)	1 (0.3)
Diverticulitis	0 (0.0)	1 (0.3)
Influenza	0 (0.0)	1 (0.3)
Klebsiella Sepsis	0 (0.0)	1 (0.3)
Pseudomonal Bacteremia	0 (0.0)	1 (0.3)
Acute Pyelonephritis	0 (0.0)	1 (0.3)
Renal Cyst Infection	0 (0.0)	1 (0.3)

In all clinical trials in the 1411 SFP-treated subjects, 143 subjects (10.1%) reported ≥1 TEAE of systemic/serious infection. The most common TEAEs of systemic/serious infection were pneumonia (1.9%), cellulitis (0.9%), sepsis (0.9%), and urinary tract infection (0.9%).

Common Adverse Events

In pooled Phase 3 studies, overall TEAEs occurred at similar frequencies between the SFP group (78.4%) and the placebo group (75.3%). The TEAEs reported by ≥3% in the SFP group and reported at least 1% more commonly in the SFP group than in the placebo group based on system organ class are listed in the Table below.

Table 48. Common Adverse Events Reported ≥3% in SFP-Treated Subjects and ≥1% More Frequent in SFP-Treated Subjects by SOC

System organ class Preferred term	SFP N=292 n (%)	Placebo N=296 n (%)
Number of subject with at least one TEAE	229 (78.4)	223 (75.3)
General Disorders and Administration Site Conditions		
Peripheral edema	20 (6.8)	11 (3.7)
Pyrexia	13 (4.5)	9 (3.0)
Asthenia	12 (4.1)	9 (3.0)
Fatigue	11 (3.8)	6 (2.0)
Infections and Infestations		
Urinary tract infection	13 (4.5)	4 (1.4)
Injury, Poisoning, and Procedural Complications		
Procedural hypotension	63 (21.6)	57 (19.3)
Arteriovenous fistula thrombosis	10 (3.4)	6 (2.0)
Arteriovenous fistula site hemorrhage	10 (3.4)	5 (1.7)
Musculoskeletal and Connective Tissue Disorders		
Muscle spasms	28 (9.6)	24 (8.1)
Pain in extremity	20 (6.8)	17 (5.7)
Back pain	13 (4.5)	10 (3.4)
Nervous System Disorders		
Headache	27 (9.2)	16 (5.4)
Respiratory, Thoracic and Mediastinal Disorders		
Dyspnea	17 (5.8)	13 (4.4)

The TEAEs reported ≥3% in the SFP group and reported more frequently in the SFP group as compared to the placebo group were procedural hypotension, muscle spasms, headache, dizziness, peripheral edema, pain in extremity, dyspnea, pyrexia, urinary tract infection, hyperkalemia, back pain, asthenia, fatigue, arteriovenous fistula site hemorrhage, arteriovenous fistula thrombosis, and hypertension. See Table below.

Table 49. TEAEs Reported ≥3% in the SFP-treated Subjects and Reported More in the SFP Group by Frequency

System organ class Preferred term	SFP N=292 n (%)	Placebo N=296 n (%)
Procedural hypotension	63 (21.6)	57 (19.3)
Muscle spasms	28 (9.6)	24 (8.1)
Headache	27 (9.2)	16 (5.4)
Dizziness	22 (7.5)	21 (7.1)
Peripheral edema	20 (6.8)	11 (3.7)
Pain in extremity	20 (6.8)	17 (5.7)
Dyspnea	17 (5.8)	13 (4.4)
Pyrexia	13 (4.5)	9 (3.0)
Urinary tract infection	13 (4.5)	4 (1.4)
Hyperkalemia	13 (4.5)	13 (4.4)
Back pain	13 (4.5)	10 (3.4)
Asthenia	12 (4.1)	9 (3.0)
Fatigue	11 (3.8)	6 (2.0)
Arteriovenous fistula thrombosis	10 (3.4)	6 (2.0)
Arteriovenous fistula site hemorrhage	10 (3.4)	5 (1.7)
Hypertension	9 (3.1)	8 (2.7)

In all clinical trials in 1411 SFP-treated subjects, 1020 of 1411 (72.3%) experienced ≥1 TEAE. The most common TEAEs were procedural hypotension (20.3%), nausea (13.0%), diarrhea (12.5%), and arteriovenous fistula site complication (12.2%). The total number of subjects who experienced a treatment-related TEAE was 136 of 1411 subjects (9.6%). The most common treatment-related TEAEs were procedural hypotension (4.2%) and nausea (1.1%).

Clinical Laboratory Findings

Iron Parameters for Possible Iron Overload:

TSAT ≥50% or Serum Ferritin ≥1200 µg/L

In the pooled Phase 3 trials, 42 (14.9%) subjects developed pre-dialysis TSAT ≥50% in the SFP group as compared to 18 (6.2%) in the placebo group in the randomized phase of the studies (see table below).

There were a few patients who developed pre-dialysis serum ferritin ≥1200 µg/L in both treatment groups (1.3% in the SFP group and 3.1% in the placebo group) during the randomized phase of the studies.

Table 50. TSAT ≥50% or Serum Ferritin ≥1200 µg/L in Phase 3 Studies

	SFP N=292 n (%)	Placebo N=296 n (%)
TSAT ≥50%	42/282 (14.9)	18/289 (6.2)

Ferritin ≥1200 µg/L	4/282 (1.4)	9/289 (3.1)

Among subjects with TSAT ≥50%, only 6 subjects had their TSAT value confirmed by 2 consecutive values measured at any time within a 2-week period (3 each in the SFP and placebo groups). In 3 of those patients (2 in the SFP group and 1 in the placebo group), study drug administration was withheld per protocol. The remaining 3 patients (1 in the SFP group and 2 in the placebo group) continued study drug treatment (see Table below).

Among subjects with serum ferritin ≥1200 µg/L, 5 subjects had their serum ferritin value confirmed by 2 consecutive values measured at any time within a 2-week period (1 in the SFP group and 4 in the placebo groups). In all 5 patients, study drug administration was withheld per protocol (see Table below).

Table 51. Subjects with Confirmed TSAT ≥50% or Serum Ferritin ≥1200 µg/L in Pooled Phase 3 Studies

	SFP N=292 n (%)	**Placebo N=296 n (%)**
TSAT ≥50%	42/282 (14.9)	18/289 (6.2)
Confirmed by 2 consecutive values measured at any time within a 2-week period (per protocol)	3/282 (1.1)	3/289 (1.0)
Study drug administration was withheld (per protocol)[a]	2/282 (0.7)	1/289 (0.3)
Continued study drug treatment	1/282 (0.4)	2/289 (0.7)
Ferritin ≥1200 µg/L	4/282 (1.4)	9/289 (3.1)
Confirmed by 2 consecutive values measured at any time within a 2-week period (per protocol)	1/282 (0.4)	4/289 (1.4)
Study drug administration was withheld (per protocol)[a]	1/282 (0.4)	4/489 (1.4)
Continued study drug treatment	0	0

[a] Defined for the purposes of this analysis as having >80% of study drug doses withheld starting within 28 days of the date of the 2nd consecutive value and ending 28 days after start of study drug withholding or at the last Stage 2 treatment period visit, whichever comes first. Withdrawal from Stage 2 within 28 days of the date of the 2nd consecutive value and not commencing Stage 3 study drug for 28 days after the last dose of study drug in Stage 2 was also counted as having had study drug withheld.

The frequency of treatment-emergent adverse events was analyzed by TSAT value and patients with TSAT ≥50% experienced slightly more overall events than those with TSAT<50% in both the SFP and the placebo groups. However, in patients with TSAT ≥50%, the frequency of events was similar between the SFP and the placebo group.

Table 52. Overall TEAEs by TSAT Value in Pooled Phase 3 Studies

	SFP		Placebo	
	TSAT≥50% N=42 n(%)	TSAT<50% N=240 n(%)	TSAT≥50% N=18 n(%)	TSAT<50% N=271 n(%)
TEAEs	35 (83.3%)	186 (77.5%)	16 (88.9%)	205 (75.6%)
TESAEs	12 (28.6%)	64 (26.7%)	7 (38.9%)	70 (25.8%)
Deaths	3 (7.1%)	8 (3.3%)	1 (5.6%)	4 (1.5%)
AEs leading to discontinuation	0 (0.0%)	11 (4.6%)	1 (5.6%)	6 (2.2%)

In all clinical trials in 1411 SFP-treated subjects, 291 (22.1%) subjects had at least one TSAT value ≥50% and 129 (9.7%) subjects had at least one serum ferritin value ≥1200 μg/L.

Liver function tests

The reported laboratory abnormalities of ALT, AST and total bilirubin in pooled Phase 3 studies is relatively low and no differences were observed between the two groups.

Table 53. Abnormalities in AST, ALT and Total Bilirubin in Pooled Phase 3 Studies

	SFP N=264 n (%)	Placebo N=266 n (%)
ALT >2 x ULN	1 (0.4)	3 (1.1)
ALT >3 x ULN	0 (0.0)	3 (1.1)
AST >2 x ULN	2 (0.8)	4 (1.5)
AST >3 x ULN	1 (0.4)	0 (0.0)
Total bilirubin >2 x ULN	0 (0.0)	1 (0.4)

In all clinical trials in 1411 SFP-treated patients, the laboratory abnormalities of ALT, AST and total bilirubin is summarized in the Table below. The overall rate is also low and there were no subjects who met the criteria for Hy's Law.

Table 54. Abnormalities in AST, ALT and Total Bilirubin in All Clinical Trials

	SFP N=1411 n (%)
ALT >2 x ULN	10/1306 (0.8)
ALT >3 x ULN	2/1306 (0.2)
AST >2 x ULN	17/1302 (1.3)
AST >3 x ULN	6/1302 (0.5)
Total bilirubin >2 x ULN	3/1306 (0.2)

Note: SFP-1 subjects are excluded from the denominators because normal ranges were not provided for that study.

Time Dependency for Adverse Events

In phase 3 trials, the treatment-emergent AEs by duration of exposure in the Phase 3 trials are shown in Table below. Overall, there was no significant difference in percentage of subjects who

experienced any TEAE across the duration of exposure intervals in the SFP groups and in the placebo groups. The most common TEAEs in subjects are included in the summary table below. The rate of procedure hypotension reported increased by the duration of exposure in the SFP group. There was no significant trend observed for other events.

Table 55. TEAEs by Duration of Exposure in Pooled Phase 3 Studies

	SFP			Placebo		
	≤12 weeks N=292	>12 to <36 weeks N=182	≥36 weeks N=78	≤12 weeks N=196	>12 to <36 weeks N=199	≥36 weeks N=76
Number of subjects with ≥1 TEAE	196 (67.1)	127 (69.8)	48 (61.5)	192 (64.9)	134 (67.3)	35 (46.1)
Procedure hypotension	43 (14.7)	29 (15.9)	16 (20.5)	37 (12.5)	33 (16.6)	8 (10.5)
Arteriovenous fistula site complication	18 (6.2)	16 (8.8)	3 (3.8)	20 (6.8)	17 (8.5)	3 (3.9)
Headache	15 (5.1)	11 (6.0)	2 (2.6)	9 (3.0)	7 (3.5)	1 (1.3)
Diarrhea	13 (4.5)	9 (4.9)	4 (5.1)	18 (6.1)	11 (5.5)	2 (2.6)
Nausea	10 (3.4)	13 (7.1)	4 (5.1)	19 (6.4)	13 (6.5)	2 (2.6)

In all clinical trials in 1411 SFP-treated patients, treatment-emergent AEs by duration of exposure by PT are summarized in the Table below. The proportion of subjects who experienced any TEAE across the duration of exposure intervals was slightly higher for the 12 to <36 weeks (81.0%) and ≥36 weeks (80.0%) intervals compared to the ≤12 weeks interval (56.3%). Similarly, the rate of procedure hypotension reported increased by the duration of exposure.

Table 56. TEAEs by Duration of Exposure in SFP-treated Patients in All Clinical Trials

	Duration of Exposure		
	≤12 weeks N=1411	12 -35 weeks N=863	≥36 weeks N=571
Number of subjects with ≥1 TEAE	795 (56.3)	699 (81.0)	457 (80.0)
Procedural hypotension	151 (10.7)	163 (18.9)	117 (20.5)
Arteriovenous fistula site complication	74 (5.2)	74 (8.6)	56 (9.8)
Headache	59 (4.2)	89 (10.3)	74 (13.0)
Diarrhea	56 (4.0)	91 (10.5)	79 (13.8)
Nausea	76 (5.4)	78 (9.0)	69 (12.1)
Diarrhea	56 (4.0)	91 (10.5)	79 (13.8)

Drug-Demographic Interactions

No study was specifically conducted to evaluate drug-demographic interactions. The following are based on subgroup analyses from clinical trials.

Age: Most patients weres <65 years of age (210 in the SFP group and 188 in the placebo group) in the safety population in pooled Phase 3 studies. There were 82 patients in the SFP group and 108 patients in the placebo group with age ≥65 years.

The frequency of TEAEs was analyzed by age group (<65 years and ≥65 years). The proportion of subjects with age ≥65 years reported slightly more overall TEAEs than those with age <65 years in the SFP group [159 (75.7%) in <65 years and 70 (85.4%) in ≥65 years]. In the placebo group, there was a similar frequency of TEAEs reported for both age groups [141 (75%) in <65 years and 82 (75.9%) in ≥65 years].

Gender: Overall, the majority of subjects in the Phase 3 Studies were males [179 (61%) in the SFP group and 196 (66%) in the placebo group]. The overall incidence of TEAEs reported in the SFP group was slightly higher in the female subjects than in male subjects (male 77.1%, female 80.5%). Similarly, the overall incidence of TEAEs reported in the placebo group was also slightly higher in the female subjects than in the male subjects (male 71.9%, female 82.0%).

Race: The overall incidence of TEAEs reported in SFP subjects was similar between Caucasian (79.2%) and non-Caucasian (77.5%). In the placebo group, the overall incidence of TEAEs was also reported similar in the Caucasian (73.5%) and non-Caucasians (77.7%).

4.2 Safety Summary

The safety of Triferic was evaluated primarily in two randomized placebo-controlled phase 3 clinical trials (SFP-4 and SFP-5) in patients with HDD-CKD. In the pooled two phase 3 trials, 292 subjects received at least 1 dose of SFP and 296 subjects received standard bicarbonate concentrate dialysate as placebo in clinical trials. The mean (SD) duration of exposure was 159.2 (112.9) days for the SFP group and 162.1 (110.9) days for the placebo group. About a half of study patients received study treatment ≥20 weeks and 20% of patients received 44-47 weeks of study treatment.

Overall, treatment-emergent adverse events (TEAEs) were reported at the similar rate between the SFP-treated patients and the placebo-treated patients (78.4% and 75.3%, respectively) during the studies. The most common TEAEs (≥3% in the SFP-treated patients) that were reported more frequently in the SFP-treated patients than in the placebo-treated patients were procedural hypotension, muscle spasms, headache, dizziness, peripheral edema, pain in extremity, dyspnea, pyrexia, urinary tract infection, hyperkalemia, back pain, asthenia, fatigue, arteriovenous fistula site hemorrhage, arteriovenous fistula thrombosis, and hypertension. Non-fatal treatment-emergent serious adverse events (SAEs) were reported at similar rates between the two groups

(24.0% in SFP-treated patients and 25.3 % in the placebo-treated patients). The nonfatal SAEs that were reported more frequently in the SFP group as compared to the placebo group included: diabetic foot infection (1% vs. 0%), arteriovenous fistula thrombosis (1.7% vs. 0.7%), and pulmonary edema (1.4% vs. 0.3%). Thirteen (4.5%) patients had at least one TEAE that leading to treatment discontinuation permanently in the SFP group as compared to 7 (2.4%) the placebo group in the clinical trials. The most common TEAEs (occurred in at least 2 subjects) leading to study discontinuation in the SFP group were asthenia, dizziness and headache.

A total of 17 deaths were reported in the two phase 3 clinical trials including 12 (4.1%) in the SFP-treated patients and 5 (1.7%) in the placebo-treated patients. Among the death cases, the duration on study treatment ranged from 8 to 328 days in the SFP-treated patients and 27 to 227 days. Time to event leading to deaths since the last hemodialysis with study drug ranged from 1 to 15 days in the SFP-treated patients and 1 to 3 days in the placebo-treated patients. Almost all patients had significant underlying cardiac conditions in addition to end-stage renal disease. Six patients in the SFP group and one patient in the placebo group died at home or nursing home without detailed information provided. The events leading to deaths were cardiac arrest in 8 cases (6 in the SFP-treated patients and 2 in the placebo-treated patients), sudden deaths or unknown cause in 5 cases (4 in the SFP-treated patients and 1 in the placebo-treated patients), acute MI in 3 cases (1 in the SFP-treated patients and 2 in the placebo-treated patients), and one case of bronchopneumonia in the SFP group. None of death cases was considered to be related to the study treatment by investigator and cases could be most likely attributed to co-morbid disease and/or disease progression.

In the two phase 3 clinical trials, suspected hypersensitivity reaction was reported in one (0.3%) patients in the SFP group as compared to none in the placebo groups (0%). The event was considered as moderate and related to study drug. Five additional cases of suspected hypersensitivity reaction were reported in phase 2 and phase 3 open-label extension treatment studies. Overall, six (0.4%) cases of suspected hypersensitivity reactions were reported in 1411 SFP-treated patients in clinical trials in the SFP development program. Two of 6 cases had events occurred at the first dose and discontinued study treatment permanently and were considered to be related to the study treatment. The remaining 4 patients continued the SFP treatment without recurrent events and are not considered to be related to the study drug.
The other adverse events of special interest including intradialytic hypotension, composite cardiovascular events, hemodialysis vascular access thrombotic event, and systemic or serious infection were similar between the SFP group and the placebo group.

A total of 1411 patients were exposed to Triferic in all clinical trials including open-label extension studies. The safety profile of Triferic in those patients was similar to that observed in Phase 3 clinical trials.

5. Considerations for the Advisory Committee

For the indication "treatment of iron loss of iron deficiency to maintain hemoglobin in adult patients with hemodialysis-dependent stage 5 chronic kidney disease (CKD 5HD)" the primary issues for efficacy for the application center around the fact that although study treatment in the two pivotal trials (SFP-4 and SFP-5) was intended to extend up to 48 weeks, in both pivotal studies fewer than 20% of patients in either treatment group (SFP or placebo) completed 48 weeks of dosing and about half of patients completed not more than 20 weeks. Consequently, there is a considerable amount of "missing data" due to study drug discontinuation by the end of the study treatment period. It is noted that a large portion of the missing data due to withdrawn patients is due to protocol-mandated changes in anemia management, which were incorporated into the protocol to protect patient safety. The large proportion of patients with early withdrawal from study treatment necessitates examination of the study data to assess impact of the early discontinuation of patients on the validity and robustness of the efficacy results.

Regarding the efficacy findings the Agency wishes the Committee to consider and discuss the following question:

- Given the extent of subjects who withdrew from the study early (including protocol mandated drop-out) and differential reasons for such early withdrawal, does the primary efficacy endpoint analysis adequately capture the benefit of the treatment? If yes, is the benefit of the treatment well estimated/established?

For the proposed labeling statement to reduce the prescribed dose of erythropoiesis stimulating agent (ESA) required to maintain desired hemoglobin levels" the sponsor has provided results of a single, exploratory Phase 2 study (NIH-FP-01).

- Considering the limitations of Study NIH-FP-01 is there substantial evidence to support the desired claim?

Safety results in the clinical studies showed some hypersensitivity events among patients treated with Triferic. There were no serious hypersensitivity reactions observed in the clinical trials. In the pivotal clinical studies in patients with hemodialysis-dependent chronic kidney disease (HDD-CKD), who have a high prevalence of comorbid conditions and underlying chronic disease, death was reported for 4.1% of SFP-treated patients and 1.7% of placebo-treated patients.

- Does the Committee have comments or recommendations regarding safety considerations for the use of Triferic if it is approved for use in the HDD-CKD population?